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IN THE
Supreme Court of the United States
OCTOBER TERM, 1994

BRISTOL-MYERS SQUIBB COMPANY,
Petitioner,
v.
ZENITH LABORATORIES, INC.,
Respondent.

Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

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PETITION FOR A WRIT OF CERTIORARI

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QUESTIONS PRESENTED

1. Whether proof of literal infringement of a patent for a new composition of matter (*e.g.*, a chemical compound) requires examination of each item of information in the patent claim, even when that information consists of scientifically redundant, overinclusive "fingerprint" data included for evidentiary identification of the patented composition, rather than restrictive conditions that precisely define and limit the patented aspects of the composition.

2. Whether a valid patent lacks protection against infringement under the doctrine of equivalents except to the extent the invention performs a function not previously performed by any prior art.

RULE 29.1 STATEMENT

Petitioner Bristol-Myers Squibb Company has no parent company. Its non-wholly owned subsidiaries are the following: Laboratoires UPSA; Nyagen; RCS Realty Corporation; Sino American Shanghai Squibb Pharma Ltd.; Squibb Nigeria Limited; UPSA Investissements; 2309 Realty Corporation; Bristol-Myers Lion Ltd.; Bristol-Myers Squibb G.M.B.H.; P.T. Squibb Indonesia; Squibb of Bangladesh Limited; Synbiotics Limited; Mead Johnson.

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PETITION FOR A WRIT OF CERTIORARI

Bristol-Myers Squibb Company hereby petitions for a writ of certiorari to review the judgment of the United States Court of Appeals for the Federal Circuit in this case.

OPINIONS BELOW

The opinion of the court of appeals (Pet. App. 1a-17a) is reported at 19 F.3d 1418. The opinions of the district court (Pet. App. 18a-74a, 75a-78a) are reported at 24 USPQ2d 1652 (D.N.J. 1992).

JURISDICTION

The court of appeals entered judgment on March 24, 1994. Pet. App. 1a. A timely petition for rehearing was denied on May 26, 1994. Pet. App. 79a-80a. On July

28, 1994, Chief Justice Rehnquist extended the time for filing a petition to and including September 14, 1994. Pet. App. 81a. This Court has jurisdiction under 28 U.S.C. § 1254.

STATUTORY PROVISIONS INVOLVED

Statutory provisions involved in the case include the following:

35 U.S.C. § 101. Inventions patentable

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

35 U.S.C. § 112. Specification

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

* * * *

35 U.S.C. § 154. Contents and term of patent

Every patent shall contain . . . a grant to the patentee, . . . for the term of seventeen years, . . . of

the right to exclude others from making, using, or selling the invention throughout the United States, and, if the invention is a process, of the right to exclude others from using or selling throughout the United States, or importing into the United States, products made by that process, referring to the specification for the particulars thereof. . . .

35 U.S.C. § 271. Infringement of patent

(a) Except as otherwise provided in this title, whoever without authority makes, uses or sells any patented invention, within the United States during the term of the patent therefor, infringes the patent.

(b) Whoever actively induces infringement of a patent shall be liable as an infringer.

* * * *

STATEMENT

The Federal Circuit in this case adopted restrictive new positions on two important and recurring aspects of patent law: the treatment of overinclusive scientific information set forth in patent claims to identify a patented new chemical compound or other composition of matter; and the meaning of the established doctrine of equivalents as a means of ensuring realistic protection against infringement commensurate with the full extent of a patent's validity. The Federal Circuit's rulings establish limitations on the scope of patent protection that are sharply out of keeping with well-settled principles of patent law. Petitioner asks this Court to grant the petition to review and to correct these rulings.

A. Background

In 1970, the Patent and Trademark Office issued a patent for a new antibiotic chemical compound called

"cefadroxil," which is effective against bacteria that are resistant to penicillin.[1] Bristol-Myers (the owner of the patent) recognized that cefadroxil in its original form could not easily be used for actual delivery of medicine to patients (or even for preliminary clinical studies) because there was no sufficiently pure or stable form of the drug. *See Bristol-Myers Co. v. U.S. Int'l Trade Comm'n*, 15 USPQ2d 1258, 1259, 1260 (Fed. Cir. 1989). Bristol-Myers scientists therefore set to work trying to produce a usable form of cefadroxil. These efforts ultimately were rewarded with the creation of a new crystal form of cefadroxil, the "Bouzard monohydrate," consisting of one water molecule for each cefadroxil molecule and named after one of the inventors, Bristol-Myers chemist Daniel Bouzard. *See id.* at 1259-60; Pet. App. 19a n.2. Bristol-Myers marketed this new drug as DURICEF.

In 1985, the Patent and Trademark Office issued a patent for this new compound—No. 4,504,657, the '657 patent. Pet. App. 2a-3a. Pursuant to 35 U.S.C. § 112, the patent contains a lengthy "specification" that describes the new crystal and how it is made and then concludes with a single "claim" that identifies the new crystal with x-ray diffraction data—"a technique," as the district court observed (Pet. App. 49a), "that in essence takes the 'fingerprint' of a crystalline compound." The claim states:

> We claim:
>
> 1. Crystalline 7-[D-α-amino-α-(p-hydroxyphenyl-) acetamido]-3-methyl-3-cephem-4-carboxylic acid monohydrate exhibiting essentially the following x-ray diffraction properties:

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[1] This was patent No. 3,489,752, referred to by the last three digits—the '752 patent. That patent expired in 1987. *See* Pet. App. 2a.

Line	Spacing d (A)	Relative Intensity
1	8.84	100
2	7.88	40
3	7.27	42
4	6.89	15
5	6.08	70
6	5.56	5
7	5.35	63
8	4.98	38
9	4.73	26
10	4.43	18
11	4.10	61
12	3.95	5
13	3.79	70
14	3.66	5
15	3.55	12
16	3.45	74
17	3.30	11
18	3.18	14
19	3.09	16
20	3.03	29
21	2.93	8
22	2.85	26
23	2.76	19
24	2.67	9
25	2.59	28
26	2.51	12
27	2.46	13
28	2.41	2
29	2.35	12
30	2.30	2
31	2.20	15
32	2.17	11
33	2.12	7
34	2.05	4
35	1.99	4
36	1.95	14
37	1.90	10

U.S. Patent No. 4,504,657, cols. 18-20 (Def. Ex. 1, Ct. App. JA 507-08). The table gives the results of directing x-rays at the crystalline powder, detecting the reflections of the x-rays from various angles (like photographing it from various angles), and recording the location and intensity of those reflections.[2]

The validity of this patent was soon tested and confirmed. When several companies sought to import the identical patented crystal into the United States, Bristol-Myers sued for injunctive relief from the International Trade Commission (ITC). The ITC denied preliminary relief, doubting the validity of the '657 patent, but the Federal Circuit reversed, rejecting the ITC's basis for questioning the validity of the patent. *Bristol-Myers Co. v. U.S. Int'l Trade Comm'n*, 15 USPQ2d 1258 (Fed. Cir. 1989). In so holding, the Federal Circuit made clear that the invention claimed was the crystal itself, with the diffraction pattern supplying information to identify this unique crystal: "The product is claimed in the '657 patent as a specific crystalline cefadroxil monohydrate, identified by its X-ray powder diffraction pattern, an accepted 'fingerprint' for crystal structure." *Id.* at 1260. *See id.* at 1260 ("new chemical structure"); *id.* at 1262 ("patentability of a new chemical structure").[3]

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[2] The "spacing d(A)" in the table stands for the location of the x-ray reflections from the crystal powder, which depend on the shape and size of the crystal lattice (unit cell); the "relative intensity" of the reflections depends on the arrangement of the atoms within the lattice. "The combination of the unit cell and the arrangement of atoms in it comprises the crystal structure itself. Therefore, the locations and relative intensities of the reflections of a crystal are characteristics of the crystal structure." L. Azaroff & M. Buerger, *The Powder Method in X-Ray Crystallography* 11 (1958); *see also United States Pharmacopeia 23* at 1843-44 (1994) (describing x-ray powder diffraction method and showing diffraction patterns).

[3] The ITC subsequently held the patent valid. *In re Certain Crystalline Cefadroxil Monohydrate*, 15 USPQ2d 1263 (ITC 1990).

B. District Court Proceedings

In 1988, respondent Zenith acquired from a Spanish company the right to distribute a compound it called "cefadroxil DC." Although Zenith's compound differs structurally from Bristol-Myers' Bouzard monohydrate in that it contains one-half of a molecule of water (a hemihydrate) for each molecule of cefadroxil, Zenith sought and obtained approval from the Food and Drug Administration to sell its drug as a generic equivalent of Bristol-Myers' already-approved Bouzard monohydrate. *See* Pet. App. 3a, 19a n.2. Zenith subsequently brought this suit against Bristol-Myers in the United States District Court for the District of New Jersey, seeking, under 28 U.S.C. § 1338, a declaratory judgment that cefadroxil DC did not infringe Bristol-Myers' '657 patent. *See* Pet. App. 4a, 19a.[4]

Bristol-Myers responded that Zenith's compound infringed its patent because cefadroxil DC does its medicinal work by actually converting into the patented Bouzard monohydrate *in vivo*—that is, in the patient's stomach. Zenith's compound, therefore, induces literal infringement in violation of 35 U.S.C. § 271(b) and also infringes Bristol-Myers' patent under the established "doctrine of equivalents," which asks whether an accused product performs substantially the same function in substantially the same way to produce substantially the same result as the patented product. *See* Pet. App. 5a, 15a, 19a; *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605, 609 (1950). Bristol-Myers relied on a host of prior precedents, not questioned by the Federal Circuit here, concluding that infringement may be found where an accused product converts *in vivo* or *in situ* into a patented product. Pet. App. 15a-16a, 61a-62a.

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[4] Earlier, Bristol-Myers had commenced an infringement action against Zenith's Spanish supplier, but that action was withdrawn when the Spanish company ceased manufacturing cefadroxil DC. Pet. App. 4a.

The district court held a six-day bench trial in which "[t]he primary factual issue . . . was whether cefadroxil DC converted *in vivo* to the Bouzard monohydrate." Pet. App. 20a.[5] Scientific witnesses on both sides testified about their experiments addressed to that factual question. *Id.* at 20a-44a. Most critical for present purposes was the testimony of Dr. Harry Brittain, particularly about his x-ray diffraction analysis. *Id.* at 48a-51a.[6] That testimony, and the district court's findings on the point (*id.* at 50a-51a), proceeded in two steps. First, Dr. Brittain showed that a sample of Bristol-Myers' product (DURICEF) was in fact the compound described in the patent: he took x-ray diffraction readings of DURICEF and matched them (21 of 22 lines, or angles) with the diffraction figures set out in the patent. *Id.* at 50a. Second, he then used the graph form of the diffraction readings for DURICEF (a diffraction pattern) as a "reference pattern" to compare with the diffraction pattern produced by certain wetted versions of Zenith's compound designed to simulate *in vivo* conditions, and he found that those patterns matched as well. *Id.* at 50a-51a. Zenith concentrated on attacking the second step by questioning whether the discovered conversion occurred in conditions that truly corresponded with stomach conditions. *Id.* at 51a-58a. Zenith did not dispute the scientific adequacy of Dr. Brittain's first step.[7]

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[5] The district court had initially "granted summary judgment in Zenith's favor on the issue of *in vivo* conversion" but immediately vacated its order and proceeded to trial. Pet. App. 19a.

[6] Dr. Brittain conducted a host of other experiments as well to determine whether cefadroxil DC converts into the Bouzard monohydrate. *See* Pet. App. 30a-41a.

[7] Dr. Brittain's generation of a "reference pattern" on his equipment was in accord with the recommended practice of the source establishing official FDA standards: "If a reference material (e.g., USP Reference Standard) is available, it is preferable to generate a primary reference pattern on the same equipment used for running the unknown sample, and under the same conditions." *United States Pharmacopeia 23* at 1844.

The district court found Bristol-Myers' "powerful proofs" to "greatly outweigh" Zenith's evidence and thus found that cefadroxil DC does in fact convert into the patented compound *in vivo*. *Id.* at 58a; *see id.* at 47a ("The Court finds that Bristol presented by far the more compelling case on the issue of conversion."); *id.* at 57a (Bristol-Myers' evidence is "simply better supported and vastly more credible"). Based on that finding, the court held that Zenith's "proposed sales of cefadroxil DC would constitute inducement of infringement under 35 U.S.C. § 271(b)." Pet. App. 66a (footnote omitted); *id.* at 66a-73a.[8] The district court entered judgment declaring Zenith's sale of cefadroxil DC an act of infringement and directing that Zenith could not sell cefadroxil DC until the date on which Bristol-Myers' patent will expire (in 2002). *Id.* at 73a-78a.

C. The Court of Appeals Decision.

The Federal Circuit reversed. Pet. App. 1a-18a. At the outset, the court rejected Zenith's argument that the '657 patent was itself limited to *pre-ingested* Bouzard monohydrate and thus, in Zenith's view, excluded Bouzard crystals that form in a patient's stomach after ingestion of cefadroxil DC. *Id.* at 6a-8a. Although Zenith contended that the scope of the patent was restricted by the Bouzard monohydrate's function of facilitating the manufacture of cefadroxil in usable form, the court made clear that this function was not an aspect of the patent: "The '657 claim is a claim for a compound. Its patentability thus derives from the *structure* of the claimed compound in relation to prior compounds. *See In re Spada*, 911 F.2d

[8] Although unnecessary to its ultimate holding, the district court rejected Bristol-Myers' alternative argument that Zenith was liable for infringement under the doctrine of equivalents. The court found "prosecution history estoppel" based on its view that Bristol-Myers had predicated its patent solely on the enhanced manufacturing properties of its invention, properties that Zenith would not use in producing the cefadroxil monohydrate *in vivo*. *Id.* at 64a-66a.

705, 708, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990). The relevance to patentability of the properties or characteristics exhibited by the compound is limited to assessing the significance of the structural distinctions of the claimed compound over the prior art." Pet. App. 7a-8a.

Having construed the '657 patent to cover any Bouzard monohydrate crystals that form *in vivo*, the court of appeals nevertheless overturned the district court's finding that there was literal infringement *in vivo*, explaining that there was an "absence of evidence comparing the '657 claim with the cefadroxil DC after ingestion." Pet. App. 12a.[9] This holding in no way questioned the district court's finding that ingested cefadroxil DC converts to DURICEF (based on a comparison of their diffraction patterns); nor did it question the *scientific* adequacy of the finding that DURICEF was the same as the compound described in the patent (based on matching of 21 of 22 diffraction lines set forth in the '657 patent and shown by the "reference pattern" produced by DURICEF). Rather, the court's holding was that proof of infringement requires, as a matter of law, a matching of the accused product and its diffraction pattern with the full set of diffraction data included in the patent claim. *Id.* at 11a-12a.[10] Explaining that "the claim is drafted in terms of x-ray diffraction lines," which therefore "set[] the metes and bounds of the invention," the court found a "failure

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[9] The court of appeals thus held simply that there was no proof that literal infringement occurred after ingestion. The court left unimpaired the district court's holding that, if literal infringement occurs *in vivo*, Zenith is liable for inducement under 35 U.S.C. § 271(b). The court of appeals' holding on this point, accordingly, is a holding entirely about the requirements for proving literal infringement.

[10] The court observed that something less than complete identity might be satisfactory, given the patent claim's use of the term "*essentially* exhibiting," but that the law "does not permit ignoring a substantial number of lines altogether," as the scientific evidence did in focusing on 22 of the 37 diffraction lines. *Id.* at 11a-12a.

of proof" because of the "improper comparison." *Id.* at 11a, 12a.

Turning from the issue of literal infringement, the Federal Circuit next held that a judgment of infringement could not rest on the doctrine of equivalents. Pet. App. 13a-17a. The court began by rejecting the district court's reasoning on this point—which relied on "prosecution history estoppel" based on Bristol-Myers' assertion of its invention's manufacturing benefits (*see* note 8, *supra*)—because "[t]here is nothing in the record indicating that the statements about manufacturing benefits played any role in the procurement of the '657 patent." *Id.* at 13a; *see id.* at 13a-15a. But the court of appeals immediately returned to the manufacturing benefits of the Bouzard monohydrate in giving its own reason for holding that "the doctrine of equivalents is inapplicable . . . as a matter of law." *Id.* at 15a.

The court ruled that, for purposes of determining whether the accused product performs substantially the same "function" as the patented invention, the only function that counts is a *new* function—one that the patented invention was the first to perform. *Id.* ("the primary, if not the only, function of the Bouzard crystal form of the drug *as compared to other forms* is to facilitate pre-ingestion manufacturing") (emphasis added); *id.* at n.9 ("the function cannot be described more broadly, i.e. as the delivery of therapeutic value to the patient, for that is the function attributable to cefadroxil *per se*, which is prior art in relation to Bouzard monohydrate"). Based on that proposition of law, the Federal Circuit ruled that "there can be no infringement under the doctrine of equivalents" in this case. *Id.* at 15a. With the focus restricted to new functions, it was irrelevant that Zenith's compound necessarily performs the same function of delivering medicine to patients as does Bristol-Myers' compound: the only relevant function was "facilitating encapsulation" for manufacturing (a function that the Federal Circuit had just concluded played no role in the

issuance of the patent), and *that* function was one Zenith's compound could not perform after ingestion. *Id.* at 15a, 17a.

The full Federal Circuit subsequently denied a suggestion for rehearing en banc. Judge Newman voted to rehear the case en banc. Pet. App. 79a-80a.

REASONS FOR GRANTING THE PETITION

The Federal Circuit rested its ruling in this case on two conclusions that, conflicting with a number of fundamental and previously clear principles of patent law, create substantial confusion about and improperly curtail the scope of patent protection. The court restricted the scope of literal infringement by equating mere identifying data (like diffraction patterns or fingerprints) with the articles that such data identify, thereby deliberately turning a blind eye to indisputable scientific evidence about how to determine when a unique chemical compound or other composition of matter is present. The court then restricted the scope of infringement under the doctrine of equivalents by limiting protection to patented inventions that perform a *new* function, thereby disconnecting the scope of infringement protection from the scope of patent validity and effectively stripping a whole range of valid patents of the essential protection to which they have long been entitled.

Each of the court's rulings is on its face broadly applicable and incompatible with otherwise-established principles of patent law. Where no intercircuit conflict is possible because of the exclusive jurisdiction of the Federal Circuit over matters of patent law, the resulting uncertainty about legal issues as fundamental as those presented here is more than enough to call for this Court's review. The Court should grant the petition to address these issues and restore the proper understanding of identifying data in patent claims and the proper concordance between infringement protection and patent validity.

I. THE FEDERAL CIRCUIT ERRONEOUSLY LIMITED THE SCOPE OF PROTECTION AGAINST LITERAL INFRINGEMENT FOR VALID PATENTS FOR NEW COMPOSITIONS OF MATTER SUCH AS CHEMICAL COMPOUNDS.

The court of appeals in this case held that it was error for a court, addressing a charge of infringement, "to compare . . . the accused product with the patentee's commercial embodiment or other version of the product or process," *even if*, as a scientific matter, the commercial product is exactly the same as the patented article. Pet. App. 11a. Thus, despite the fact that Bristol-Myers established to a scientific certainty that its product was the same as the compound identified in the patent, and further established that Zenith's compound (cefadroxil DC *in vivo*) was the same as that product, the court of appeals nonetheless reversed the district court's finding of infringement, holding that as a matter of law the accused product has to be directly compared to the full set of identifying data in the patent. *Id.* at 11a-12a. If this rule of law were to stand, it would mean that a patent holder, to prove infringement, would have to compare the infringing product to each and every piece of identifying data in the patent claim even when a far less burdensome comparison would irrefutably establish that the two compounds were identical. There is simply no sound basis for engrafting this requirement onto the structure of existing patent law.

The Federal Circuit's ruling fundamentally confuses two different types of patent claims and imposes a new limitation on a type of patent claim where it does not belong. Where the full set of limitations set forth in a patent claim *restrictively defines* what is new about the invention—as when a new machine is built and the claim precisely specifies the novel aspects of it—then it is undoubtedly correct that each of those limitations must be "read on" an accused product to establish literal infringement. But where the data in the claim serve merely to

identify or *describe* what is concededly a new invention, and such data are in scientific terms more than necessary (overinclusive, excessive) for that purpose, then the Federal Circuit's rule is erroneous. In that circumstance, which is a common one—*e.g.*, when a never-before-created chemical compound or other composition of matter is the patented invention and the patent claim simply gives scientists the tell-tale signs to determine if what they have produced is the new compound or composition—the court's rule mistakenly equates the object patented with information that is only of evidentiary significance in determining when that object has been found.

This error is the equivalent of requiring, as a matter of law, a matching of every ridge, whorl, loop, and other characteristic of a detailed fingerprint to prove that an "accused" finger is the same as a known finger—even though the science of fingerprint identification establishes the indisputable sufficiency of far less information. *See* P. Giannelli & E. Imwinkelried, *Scientific Evidence* § 16-7 (1986). When there is no question about what the object of identification is (*e.g.*, a finger of a particular person), it is a scientific question how much of a particular form of evidence (*e.g.*, fingerprint information) is sufficient to establish the identification. And when there is more such evidence than is scientifically necessary to establish the identification, it is senseless to ignore the redundant character of the data and require jot-by-jot scrutiny of every item.

The x-ray diffraction data in a patent like '657 are, as the district court and Federal Circuit both recognized, just like "fingerprint" evidence. Pet. App. 49a; *Bristol-Myers Co. v. ITC*, 15 USPQ2d at 1260. It does not *restrict* and *define* the patented aspects of a physical object, but merely supplies data for *identifying* the object that is patented—namely, the chemical compound itself. Indeed, the Federal Circuit, both in its opinion on the validity of the '657 patent and elsewhere in its opinion under review here, expressly recognized that the thing patented was the

crystal structure itself (the Bouzard monohydrate). Pet. App. 7a ("The '657 claim is a claim for a compound."); page 6, *supra* (quoting validity opinion). It is therefore fundamentally a factual *scientific* question how much diffraction data (or, in a different case, other types of data) are needed to answer the central question of infringement analysis—whether the accused product and the patented product are "the same." *Union Paper-Bag Machine Co. v. Murphy*, 97 U.S. 120, 125 (1878). *See Fromberg, Inc. v. Thornhill*, 315 F.2d 407, 411 (5th Cir. 1963); *Intervet America, Inc. v. Kee-Vet Labs., Inc.*, 887 F.2d 1050, 1053 (Fed. Cir. 1989) ("infringement is a question of fact").

Yet the Federal Circuit did not question—what is indeed beyond dispute—that as a scientific matter 37 diffraction lines are grossly overinclusive, or redundant, for identification purposes.[11] The court nevertheless treated

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[11] For example, the *United States Pharmacopeia 23*, which sets forth official FDA standards, states that "[i]dentification of crystalline materials can be accomplished by comparison of X-ray powder diffraction patterns obtained for known materials with those of the unknown" and "[i]t is generally sufficient [to establish identity] to scan past the ten strongest reflections" in a diffraction pattern. *Id.* at 1844 (footnote omitted). Zenith's own experts testified to the scientific sufficiency, for identification purposes, of looking at "maybe 15 or 20" lines (Ct. App. JA 2075 (Dr. Pfeiffer)) or even three lines if they are strong enough (Ct. App. JA 2918 (Dr. Greenblatt)). The 21 lines relied on in this case by Bristol-Myers' expert and the district court included the strongest, most significant lines.

Beyond that, there was no serious dispute as a scientific factual matter that DURICEF was the same as the invention described in the '657 patent. Zenith's expert Dr. Greenblatt so testified in her deposition. Ct. App. JA 1567, 1570-71. An FDA report submitted by Zenith stated that the diffraction pattern for Bristol-Myers' product "agrees with the data presented by the Bouzard patent." Ct. App. JA 237. The ITC stated in its opinion upholding the validity of the '657 patent that Bristol-Myers' "commercially successful product . . . is the invention claimed in the '657 patent." *In re*

the diffraction data as if each element of it imposed an additional limitation on the protected invention. That treatment, which is scientifically incorrect, necessarily establishes what Zenith described as "a ruling of law . . . as a matter of claim interpretation" (Response to Reh'g Pet'n at 5) that the patented invention in this common situation is not the chemical itself, but each and every piece of identifying data. The Federal Circuit's ruling is thus contrary to the court's own prior recognition in this very case. More basically, it violates the cardinal principle that patent claims should be construed "in the light . . . of scientific fact." *Smith v. Snow*, 294 U.S. 1, 14 (1935).[12]

The Federal Circuit's new treatment of chemical patents and diffraction data is, in fact, flatly inconsistent with the (otherwise-binding) precedent of its predecessor court. In *In re Papesch*, 315 F.2d 381, 391 (Ct. Cust. Pat. App. 1963), the court stressed the very distinction the Federal Circuit here ignored: "a formula is not a compound and while it may serve in a claim to *identify* what is being patented, as the metes and bounds of a deed identify a plot of land, the *thing* that is patented is not the formula but the compound identified by it." More specifically, in *In re Grose*, 592 F.2d 1161 (Ct. Cust. Pat. App. 1979), the court discussed "[t]he significance of differences in X-ray diffraction data" where a patent claim for a chemical compound (a "zeolite"), using language materially indistinguishable from the claim here,

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Certain Crystalline Cefadroxil Monohydrate, 15 USPQ2d at 1270. And Zenith's amended complaint (at ¶ 30) described Bristol-Myers' product as "covered by the '657 patent." Ct. App. JA 202.

[12] To the extent that the Federal Circuit was establishing a special *evidentiary* rule—one that disregards scientific standards of evidentiary sufficiency—it plainly has no authority to depart from the Federal Rules of Evidence that govern all cases in district courts. *See* Fed. R. Evid. 101, 1101, 1102; 28 U.S.C. § 2072; *SRI Int'l v. Matsushita Elec. Corp.*, 775 F.2d 1107, 1116 (Fed. Cir. 1985).

"followed the apparently universal practice in this art of 'fingerprinting' the crystal structure of their zeolite through a characteristic X-ray powder diffraction pattern." *Id.* at 1165.[13] In comparing the claimed crystal with another, the court stated:

> X-ray powder diffraction data are merely an analytical tool for identifying polycrystalline materials according to differences in crystal structure. The ultimate question, in ascertaining whether a particular zeolite is a different species from those of like chemical composition, is whether it has the same crystal structure. Appellants are claiming a crystal structure. Thus, we are concerned not with whether there are differences in d-spacing values and relative intensities, but with whether such differences support a conclusion that [the two compounds] have different crystal structures.

Id. at 1165-66 (footnote omitted). That approach to construing a claim for a compound that recites diffraction data, and to comparing the compound with another chemical compound, respects sound science. The Federal Circuit ruling in this case is fundamentally inconsistent with that approach.

The ruling below not only is incorrect but also will have harmful consequences. Owners (or future seekers) of patents for chemical compounds or other compositions of matter will now be limited, or at a minimum have to guess which authority will govern, in their efforts to secure protection against infringement for their inventions. This impairment—with the inevitable waste and difficulties in having to prove infringement through efforts to match every bit of scientifically redundant data in a pa-

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[13] The patent claim stated that a particular compound had "an X-ray powder diffraction pattern containing *at least* those d-spacings set forth" in a table included in the claim. 592 F.2d at 1162 (emphasis added).

tent claim [14]—will immediately affect a large number of chemical patents. With respect to the use of diffraction data alone, which is a standard procedure (*see In re Grose*, 592 F.2d at 1165), the decision affects the approximately 400 unexpired patents for chemical compounds that recite diffraction data.[15] And the principle adopted by the Federal Circuit applies not just to diffraction data but equally to any other form of scientific "fingerprint" data.[16]

The Federal Circuit's ruling also produces immediate uncertainty for claimants seeking new patents. If patent owners are to be penalized for overinclusive identifying data in their patent claims, they will spend needless resources attempting to predict not only what language the Patent and Trademark Office will accept but also what data will simultaneously serve the two essential purposes of the patent claim: to be inclusive enough to identify the invention and thus afford protection against infringement, while not being so overinclusive as to make enforcing the patent over its 17-year life wastefully expensive (through, *e.g.*, compelled redundancy of scientific proof) or perhaps impossible. The drafting of claims is

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[14] Here, for example, present-day accepted methodology for x-ray diffraction analysis would not produce the full set of 37 diffraction readings included in the '657 claim. Given the undisputed scientific adequacy of the diffraction-pattern matching produced by current equipment, it would be purely wasteful of the time and resources of scientists, inventors, and courts (and in other cases perhaps impossible) to insist on examination of even concededly redundant data in the patent.

[15] A computer search on Dialog discloses roughly that number of patents using diffraction data issued during the past 17 years (the term of patents).

[16] For chemical compounds alone, such data include infrared spectra, nuclear magnetic resonance spectra, data about solubility and melting points, and "elemental analysis" information. *See, e.g.*, R. Faber, *Landis on Mechanics of Patent Claim Drafting* § 52 (3d ed. 1990).

already difficult and costly [17]; a judicial refusal to accept scientific reality in reading and applying claim language for infringement purposes senselessly adds new difficulties and costs, and thus unjustifiably weakens the meaningful economic protection that patent law is designed to afford inventors.

The Federal Circuit's ruling harms persons other than the patent owner as well. If patent claimants are penalized for overinclusion of information in their claims, they must seek to reduce the information supplied to the bare minimum that will suffice for protection—*e.g.*, to give the minimal amount of diffraction data needed for identification. The inevitable result of holding back information is to make it more difficult for the public to identify the patented invention. But that result is squarely contrary to the basic purpose of the requirement of written descriptions in patents: to provide as much information as possible for the public to be able to identify the invention, both to avoid infringement during the term of the patent and to reproduce the invention once the patent has expired. *See* 35 U.S.C. § 112; 37 C.F.R. § 1.71; *Schriber-Schroth Co. v. Cleveland Trust Co.*, 305 U.S. 47, 57 (1938). The Federal Circuit's rule—as applied to the range of cases where the patented invention is a new chemical compound or other composition of matter and the information set forth in the claim serves redundantly

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[17] *See Topliff v. Topliff*, 145 U.S. 156, 171 (1892) ("The specification and claims of a patent, particularly if the invention be at all complicated, constitute one of the most difficult legal instruments to draw with accuracy."); *Georgia-Pacific Corp. v. United States Plywood Corp.*, 258 F.2d 124, 136 (2d Cir.), *cert. denied*, 358 U.S. 884 (1958) ("the policy of the patent statute contemplates granting protection to valid inventions, and this policy would be defeated if protection were to be accorded only to those patents which were capable of precise definition"; inventions "cannot always be described in terms of exact measurements, symbols and formulae"); E. Thomas, *Chemical Inventions and Chemical Patents* § 9 (Auslander ed. 1964) (a chemical invention presents a special "difficulty of interpreting and describing something invisible").

to identify, but not to restrict, the invention—would thus perversely penalize patent claimants for oversupplying information: it "would foster concealment rather than disclosure of inventions, which is one of the primary purposes of the patent system." *Graver Tank*, 339 U.S. at 607. This topsy-turvy result should not stand.

II. THE FEDERAL CIRCUIT ERRONEOUSLY LIMITED PROTECTION AGAINST INFRINGEMENT UNDER THE DOCTRINE OF EQUIVALENTS TO PATENTS FOR INVENTIONS THAT PERFORM NEW FUNCTIONS.

In holding the doctrine of equivalents inapplicable here, the Federal Circuit ruled simply that the doctrine's threshold requirement (that the patented product and the accused product perform substantially the same "function") is limited to *new* functions of the invention—those it performs "as compared to" those performed by "prior art." Pet. App. 15a & n.9. Under that ruling, a perfectly valid patent for an invention that does not perform any new function has no protection against infringement under the doctrine of equivalents. This startling result is contrary to established precedents and principles of patent law.

Most specifically, this Court and the Federal Circuit itself, in applying the doctrine of equivalents, have identified the "function" of a patented invention in terms making clear that it need *not* be one never before performed by prior art. For example, in *Graver Tank*, this Court identified "welding" as the function for purposes of the longstanding function/way/result test. 339 U.S. at 611.[18] In *Spectra Corp. v. Lutz*, 839 F.2d 1579 (Fed.

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[18] "The trial judge found on the evidence before him that the Lincolnweld flux [the accused product] and the composition of the patent in suit are substantially identical in operation [way] and in result. He found also that Lincolnweld is in all respects equivalent to Unionmelt [the patented product] for welding purposes [func-

Cir. 1988), the court identified the function as "dyeing." *Id.* at 1582 ("The function (dyeing) and the result (dyed material) are broadly the same."). Plainly, neither function was original to the patented inventions at issue. Similarly, in *Carman Indus., Inc. v. Wahl*, 724 F.2d 932 (Fed. Cir. 1983), the court made explicit that the invention's function ("to promote the flow from the [storage] bin or hopper of solids that have poor flow characteristics") was far from new: the court described the "[p]rior art approaches to" performing the same function. *Id.* at 934 ("Prior art approaches to the problem of promoting the flow of difficult-to-handle solids involve the use of sweep arms, screw conveyors, or like elements."). The Federal Circuit's ruling in the present case is flatly inconsistent with those standard applications of the doctrine of equivalents.

More broadly, the Federal Circuit's ruling, by stripping a large class of valid patents of an important protection against infringement, violates the bedrock principle that protection against infringement should be commensurate with the validity of the patent. For example, the Federal Circuit has recognized that "claims must be given the *same* construction when considering infringement as when considering validity." *Intervet America*, 887 F.2d at 1053; *see Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1554 (Fed. Cir. 1983); *Lerner v. Child Guidance Prods., Inc.*, 547 F.2d 29, 31 (2d Cir. 1976); *Leeds & Northrup Co. v. Doble Eng'g Co.*, 159 F.2d 644 (1st Cir.

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tion]." 339 U.S. at 611; *see also Union Paper-Bag Machine Co. v. Murphy*, 97 U.S. at 126 ("cutting" function).

The doctrine of equivalents, with its function/way/result test, traces its lineage well back into the nineteenth century. *See Graver Tank*, 339 U.S. at 608-09, citing, *e.g.*, *Sanitary Refrigerator Co. v. Winters*, 280 U.S. 30 (1929), *Westinghouse v. Boyden Power Brake Co.*, 170 U.S. 537 (1898), *Union Paper-Bag Machine Co. v. Murphy, supra*, *Winans v. Denmead*, 56 U.S. (15 How.) 330 (1854); *Gray v. James*, 10 F. Cas. 1015, 1016 (C.C.D. Pa. 1817) (No. 5718) (Washington, J.); *Odiorne v. Winkley*, 18 F. Cas. 581, 582 (C.C.D. Mass. 1814) (No. 10,432) (Story, J.).

1947). It is equally well recognized that the doctrine of equivalents is to be applied in light of prior art precisely to ensure that the realistic protection afforded by the doctrine reaches no farther than, but as far as, what is claimed as new—*i.e.*, patentable—in the patented invention. *See Wilson Sporting Goods Co. v. David Geoffrey & Assoc.*, 904 F.2d 677, 684 (Fed. Cir.), *cert. denied*, 498 U.S. 992 (1990); *Read Corp. v. Portec, Inc.*, 970 F.2d 816, 822 n.2 (Fed. Cir. 1992) ("Equivalency to limitations of the claim must be the focus of the [doctrine of equivalents] inquiry."); *Carman Indus.*, 724 F.2d at 937 n.5. *See also Ziegler v. Phillips Petroleum Co.*, 483 F.2d 858, 869 (5th Cir.), *cert. denied*, 414 U.S. 1079 (1973) ("The nature of the invention determines the breadth of its protection under the doctrine of equivalents. Because the doctrine rests on equitable considerations, the principle has developed that an inventor, with respect to his patent, is entitled to a range of equivalents commensurate with the scope of his invention." (citing cases)). The law could hardly be otherwise: the value of a valid patent *is* the right it gives the owner to preclude others from infringement. 35 U.S.C. § 154 (patent gives owner "the right to exclude others from making, using, or selling the invention"), § 271(a) (infringement occurs when anyone "without authority makes, uses or sells any patented invention").

Yet it is beyond dispute that an invention need not perform a new function to be validly patentable. The requirements of utility, novelty, and nonobviousness (35 U.S.C. §§ 101, 102, 103) do not, as a matter of plain English or common sense, incorporate a demand that the use of the invention be a new one: a different apparatus or compound that performs the same function as an existing one (like a new medicine for an ailment currently treated by an existing drug) can be useful, novel, and nonobvious. That, indeed, is why "pioneer patents"—for inventions that perform "a function never before performed"—are recognized as only one special subtype, not

the universe, of valid patents. *Westinghouse v. Boyden Power Brake Co.*, 170 U.S. 537, 561-62 (1898); *see Morley Sewing-Machine Co. v. Lancaster*, 129 U.S. 263, 273 (1889).

Not surprisingly, the Federal Circuit and its predecessor court have repeatedly recognized that it is a mistake to require a new invention to perform a new function (or operation). The Court of Customs and Patent Appeals specifically held that "whether a given chemical compound or composition has the same usefulness" as a prior product (though potentially relevant as an evidentiary matter to the issue of obviousness) is *not* a requirement for patent validity. *In re Cofer*, 354 F.2d 664, 667 (1966). More recently, the Federal Circuit stressed that "there is no requirement . . . that [the patent owner] show 'operational differences' of the claimed device over the prior art. . . . [A]pparatus claims cover what a device *is*, not what a device *does*. An invention need not *operate* differently than the prior art to be patentable, but need only *be* different." *Hewlett-Packard Co. v. Bausch & Lomb, Inc.*, 909 F.2d 1464, 1468 (1990) (footnote omitted).[19] The Federal Circuit has even recognized that a patent, to be valid, need not perform an old function in an *improved* manner. *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1390, *cert. denied*, 488 U.S. 956 (1988)[20]; *see In re Casey*, 370 F.2d 576, 580 (Ct. Cust.

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[19] Patents fall into two groups: those where what is patented is an apparatus, machine, device, composition of matter, or other physical object; those where what is patented is a process or other physical operation. *See* P. Rosenberg, *Patent Law Fundamentals* § 6.01[2], at 6-25 (2d ed. 1994). The Federal Circuit's reference to "apparatus claims" in *Hewlett-Packard* distinguishes "process claims," where it is the function performed that is the subject of the patent. The patent at issue here, as the Federal Circuit itself observed in rejecting Zenith's effort to restrict it to manufacturing properties, is for a physical object, like the apparatus claim in *Hewlett-Packard*, not for a process.

[20] "The patent statute does not require that a patentable invention be superior to all prior devices. *Custom Accessories, Inc. v.*

Pat. App. 1967). In this very case, moreover, the Federal Circuit recognized in another portion of its opinion that a new compound need not perform a new operation or function to be patentable: "Its patentability thus derives from the *structure* of the claimed compound in relation to prior compounds," not from its "properties." Pet. App. 7a-8a (citing *In re Spada*, 911 F.2d 705, 708 (Fed. Cir. 1990)).

The Federal Circuit's new view of the doctrine of equivalents necessarily casts aside this well-established law. Unless the Federal Circuit meant *sub silentio* to introduce a new condition on issuance of a valid patent (namely, that the invention perform a new function)—which it could not properly do—the ruling below necessarily severs the scope of protection against infringement from the scope of patent validity, depriving a class of indisputably valid patents of full protection against infringement. The decision thus dramatically curtails the realistic protection to which all valid patents have long been entitled and throws into confusion the continuing validity of long-settled principles of patent law.[21]

Jeffrey-Allan Industries, Inc., 807 F.2d 955, 960 n.12, 1 USPQ2d 1196, 1199 n.12 (Fed. Cir. 1986) ('Finding that an invention is an "improvement" is not a prerequisite to patentability'); G. Rich, *Principles of Patentability*, 28 Geo.Wash.L.Rev. 393, *reprinted in* 42 J.Pat.Off.Soc'y 75 (1960) (discussing 'the unsound notion that to be patentable an invention must be better than the prior art')." 851 F.2d at 1390.

[21] The Federal Circuit's holding disregards another, closely related, well-established principle of patent law: that the owner of a non-process patent (like the "composition of matter" patent here) is entitled to a monopoly on *every* use of the invention during the term of the patent. *See Potts v. Creager*, 155 U.S. 597, 606 (1895) ("Doubtless a patentee is entitled to every use of which his invention is susceptible, whether such use be known or unknown to him."); *Radio Corp. of America v. Radio Eng'g Lab., Inc.*, 293 U.S. 1, 14 (1934); *Roberts v. Ryer*, 91 U.S. 150, 157 (1875) ("The inventor of a machine is entitled to all the uses to which it can be put, no matter whether he had conceived the idea of the use or

The protection stripped from a large range of inventions is of dramatic significance. Many and perhaps most patents involve inventions that perform old functions: again, that is what makes pioneer patents distinctive.[22] And the doctrine of equivalents, far from being a minor appendage to the guarantee against literal infringement, is so fundamental to patent law that it has been described as stating "[t]he critical test in any infringement suit." A. Miller & M. Davis, *Intellectual Property: Patents, Trademarks, and Copyright in a Nutshell* 124 (2d ed. 1990); *see id.* at 126. Indeed, this Court has said that, without the "wholesome realism" of the protection furnished by the doctrine of equivalents, a patent would be a "hollow and useless thing." *Graver Tank*, 339 U.S. at 608, 607. Because "minor deviations in the structure of almost any invention could be devised to elude the reach of the patent's protection, . . . a patent would be virtually worthless if it did not protect against devices which incorporate unimportant variations of the patented device." *Ziegler*, 483 F.2d at 868; *see Graver Tank*, 339 U.S. at 607 ("Outright and forthright duplication is a dull and very rare type of infringement. To prohibit no other would place the inventor at the mercy of verbalism and would be subordinating substance to form.").

The Federal Circuit's ruling is anything but the sort of finetuning of patent-law principles, or settling of rules where clarity is as important as content, that this Court should leave to that court for final determination. Rather, the ruling destroys a fundamentally important protection

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not."); *SRI Int'l*, 775 F.2d at 1123. In this case, the Federal Circuit, while recognizing the validity of the '657 patent, denied Bristol-Myers the right to control one use of that very invention—as medicine *in vivo*.

[22] Most patents are not pioneer patents and hence do not perform "a function never before performed" (*Westinghouse*, 170 U.S. at 561-62). *See National Hollow Brake-Beam Co. v. Interchangeable Brake-Beam Co.*, 106 F. 693, 710-11 (8th Cir. 1901); 6. E. Lipscomb, *Walker on Patents* § 22:41, at 557-58 (3d ed. 1987).

for a significant class of valid patents. This Court should grant the petition to review and reverse the Federal Circuit's ruling.

CONCLUSION

The petition for a writ of certiorari should be granted.

Respectfully submitted,

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Dated: September 14, 1994

APPENDICES

APPENDIX A

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

92-1527

ZENITH LABORATORIES, INC.,
Plaintiff-Appellant,

v.

BRISTOL-MYERS SQUIBB COMPANY,
Defendant-Appellee.

Appealed from U.S. District Court
for the District of New Jersey
Judge Wolin

Decided: March 24, 1994 [corrected March 31, 1994]

Before PLAGER, CLEVENGER, and SCHALL, *Circuit Judges.*

PLAGER, *Circuit Judge.*

The question in this declaratory judgment action is whether a drug compound, which in its manufactured state does not infringe the patent in suit, becomes infringing as a result of transitory chemical changes that occur *in vivo,* that is, as a result of ingestion by the patient. There are fact issues—what changes actually occur when the drug is ingested, and how do we know;

there are legal issues—does a compound that changes in the human body into the patented product on its way to becoming the active ingredient in the drug (the original patent on the active ingredient having earlier expired) literally infringe, infringe under the doctrine of equivalents, or infringe by inducement.

The District Court for the District of New Jersey, Civil Action No. 91-3423, entered judgment, following a bench trial, that plaintiff/appellant Zenith Laboratories, Inc.'s (Zenith) commercial sale of cefadroxil DC induces infringement of U.S. Patent 4,504,657 (the '657 patent),[1] the patent at issue. *Zenith Lab. Inc. v. Bristol-Myers Squibb Co.*, 24 USPQ2d 1652 (D.N.J. 1992) (*Zenith II*). The '657 patent is owned by Bristol-Myers Squibb Co. (Bristol). For the reasons set forth, we reverse.

BACKGROUND

The chemical compound cefadroxil, an antibiotic of the cephalosporin family effective against bacteria that are resistant to penicillin, was described and claimed in United States Patent No. 3,489,752 (the '752 patent), which issued in 1970; the owner was Bristol. The claims of the '752 patent covered any and all forms of cefadroxil—they described the chemical compound *per se*. The '752 patent expired in 1987.

In the meantime, Bristol set to work to find a commercially useful crystalline form of the compound that would overcome problems related to manufacture of the product so that it would be usable by humans. The task of developing a commercial production process was assigned to certain of Bristol's chemists. They developed what became known as the Bouzard monohydrate, named after one of the discoverers—a new crystalline form of cefadroxil. Unlike prior forms of cefadroxil, Bouzard

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[1] That patent issued March 12, 1985, and thus will expire on March 12, 2002.

monohydrate possesses certain characteristics in its pre-ingested, powdered form, related to bulk density, solubility, and stability (manufacturing-related characteristics), which make it particularly suitable for packaging into capsules.

The Bouzard monohydrate was the subject of the single claim in the '657 patent:

> 1. Crystalline 7 - [D-α-amino-α-(p-hydroxyphenyl-) acetamido]-3-methyl-3-cephem-4-carboxylic acid monohydrate exhibiting essentially the following x-ray diffraction properties: [a 37-line table of relative intensities exhibited by Bouzard monohydrate at various scan angles].

In July 1988, Zenith, the plaintiff in this declaratory judgment action, contracted with a Spanish company, Gema, S.A. of Barcelona (Gema), to become the exclusive United States distributor of the form of cefadroxil manufactured by Gema and known as cefadroxil DC. Cefadroxil DC is a hemihydrate form of cefadroxil and thus differs structurally from Bouzard monohydrate.[2] Zenith and Gema then undertook to obtain approval from the Food and Drug Administration (FDA) for commercial marketing in the United States of cefadroxil DC. Pursuant to FDA regulations, Zenith and Gema sought abbreviated approval on the grounds that cefadroxil DC was bioequivalent to a form of cefadroxil monohydrate (other than Bouzard monohydrate) which had already been approved by the FDA for commercial sale. In October 1990, the FDA granted approval.[3]

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[2] The difference is the number of water molecules which are paired with each cefadroxil molecule.

[3] The record suggests that the FDA subsequently reconsidered and rescinded this approval after Bristol filed with the FDA a citizens petition seeking to block approval on the grounds cefadroxil DC was a hemihydrate and thus not bioequivalent to cefadroxil monohydrate. The record does not indicate whether the FDA thereafter approved Zenith's application.

In June 1991, after learning of Zenith's and Gema's efforts to obtain FDA approval, Bristol filed suit against Gema (and Gema's affiliates) in the District Court for the District of Maryland, Civil Action No. HAR 91-1765 (the Maryland action), alleging infringement of the '657 patent. Subsequently, when Gema announced it was abandoning its plans to manufacture cefadroxil DC, that suit was dismissed upon stipulation of the parties.

Zenith then, in August 1991, filed the present declaratory judgment action against Bristol in the District Court for the District of New Jersey. Zenith's complaint contained four counts. In count one, Zenith sought a declaration that cefadroxil DC does not infringe the '657 patent, and in count two, a declaration that Bristol is equitably estopped from asserting that cefadroxil DC infringes the '657 patent. In count three, Zenith alleged that Bristol, by initiating the Maryland action, violated a consent decree previously entered in settlement of prior litigation between the parties; and in count four, that Bristol had engaged in unfair competition. (Zenith subsequently added a fifth and still pending count alleging that Bristol had committed antitrust violations.)

Bristol then moved to dismiss counts one and two, and for summary judgment on counts three and four. Zenith filed cross-motions for summary judgment on these counts. On December 12, 1991, the trial court granted Bristol's motion to dismiss count three (concerning the prior consent decree) on the ground that the count was moot in view of the previous dismissal of the Maryland action. *Zenith Lab. Inc. v. Bristol-Myers Squibb Co.*, 24 USPQ 2d 1641, 1651 (D.N.J. 1991) (*Zenith I*). As to Zenith's motion for summary judgment on count one (the infringement count), the court stayed that motion pending an oral hearing. *Id.* at 1648. The court denied all other motions. *Id.* at 1648, 1650-51.

At the hearing on the infringement count, Bristol conceded that cefadroxil DC, being a hemihydrate, did not

literally infringe the '657 patent in its pre-ingested form. Bristol nevertheless argued that Zenith was liable under the patent on two grounds; Zenith's product infringed under the doctrine of equivalents; and Zenith's product converted into the patented compound in the patient's stomach, and thus the sale of cefadroxil DC would induce infringement of the '657 patent under 35 U.S.C. § 271(b) (1988). The trial court concluded that summary judgment was appropriate since Bristol had not raised a genuine factual dispute on these issues; and on March 4, 1992, the court granted Zenith's motion for summary judgment on count one.

However, subsequently, on April 16, 1992, upon Bristol's motion for reconsideration, the court vacated its March 4, 1992 decision. The court denied Zenith's motion for summary judgment on count one on the basis that Bristol, through two declarations submitted with its motion for reconsideration, had demonstrated a genuine dispute on the *in vivo* conversion issue. Consequently, it ordered that that count be severed from the remaining counts and tried separately.

From May 26, 1992 through June 5, 1992, the court conducted a bench trial on count one. Following the trial, the court rejected Bristol's theory of infringement under the doctrine of equivalents. It found that Bristol, through prosecution history estoppel, had relinquished coverage of cefadroxil DC. However, the court found that cefadroxil DC converts to Bouzard monohydrate in the patient's stomach. Since an act of literal infringement thus occurs in the patient's stomach as a result of ingestion of cefadroxil DC, the court concluded that Zenith's sale of cefadroxil DC would induce infringement of the '657 patent.

On August 6, 1992, the court, in accordance with its findings and conclusions, entered judgment for Bristol. *Zenith II*, 24 USPQ2d 1652. The court, pursuant to 35 U.S.C. § 271(e)(4)(A) (1988), ordered that the effec-

tive date of any approval by the FDA of cefadroxil DC for commercial distribution and sale by Zenith could be no earlier than March 12, 2002, the expiration date of the '657 patent. *Id.* at 1676. It subsequently certified the finality of that judgment pursuant to Rule 54(b) of the Federal Rules of Civil Procedure. Zenith then filed this appeal.

DISCUSSION

Zenith presents five separate grounds on which the judgment of the trial court should be reversed. First, the claim of the '657 patent, properly construed, does not cover Bouzard crystals which might form momentarily in a patient's stomach. Second, even assuming conversion *in vivo* is within the scope of the claim, there was a failure of proof as to whether any crystals, formed in the stomach from ingested cefadroxil DC, literally infringe the '657 patent. Third, even if such crystals formed, there would be no infringing "use" within the meaning of 35 U.S.C. § 271(a) (1988). Fourth, the doctrine of equivalents, applied in reverse, precludes a judgment of literal infringement. And fifth, the court erroneously declined to grant summary judgment that Bristol was equitably estopped from asserting that cefadroxil DC infringed the Bouzard patent.

1.

We begin with claim construction: whether the claim of the '657 patent, properly construed, covers Bouzard crystals which might form momentarily in a patient's stomach. Zenith argues that, due to statements made by Bristol during the '657 prosecution, the '657 claim is limited to the pre-ingested, powdered form of Bouzard monohydrate. In those statements Bristol particularly emphasized the superior manufacturing-related benefits of the pre-ingested form of Bouzard monohydrate in relation to prior forms of cefadroxil. Bristol, it is argued, thus relinquished coverage of any forms of cefadroxil DC that do not exhibit these manufacturing-related characteristics

—that would obviously include any Bouzard monohydrate formed in a patient's stomach.

Zenith has a point. Prosecution history serves as a limit on the scope of claims by excluding any interpretation of the claim language that would permit the patentee to assert a meaning for the claim that was disclaimed or disavowed during prosecution in order to obtain claim allowance. *Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 452, 227 USPQ 293, 296 (Fed. Cir. 1985). The prosecution history in this case is replete with arguments by Bristol that the importance of this invention was the discovery of a way to manufacture the known compound so as to make it commercially available for medical treatment.

The difficulty with Zenith's argument, however, is in the nature of the sole claim in the patent. The claim as written and allowed simply describes a compound having specified chemical properties. The question before us is not one of validity: whether the claim would be patentable over the prior art if the suggested restriction were not applicable. The question here is one of infringement: whether there is anything in the claim as issued that limits it to the pre-ingested form, keeping in mind the principle that it is improper to read a limitation into a claim "wholly apart from any need to interpret what the patentee meant by particular words or phrases in the claim." *E.I. Du Pont de Nemours & Co. v. Phillips Petroleum Co.*, 849 F.2d 1430, 1433, 7 USPQ2d 1129, 1131 (Fed. Cir.), *cert. denied*, 488 U.S. 986 (1988).

Zenith nonetheless argues that the term "properties" in the claim is the vehicle for incorporating its proposed restriction into the claim. But that term plainly refers to *x-ray diffraction* properties. X-ray diffraction properties have nothing to do with the manufacturing benefits which Bristol highlighted.

Zenith's argument suffers from additional infirmities. The '657 claim is a claim for a compound. Its patentabil-

ity thus derives from the *structure* of the claimed compound in relation to prior compounds. *See In re Spada*, 911 F.2d 705, 708, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990). The relevance to patentability of the properties or characteristics exhibited by the compound is limited to assessing the significance of the structural distinctions of the claimed compound over the prior art. Second, as we later note in more detail, it is not at all clear that the statements concerning these characteristics played a determinative or even significant role in the Patent and Trademark Office's (PTO's) decision to grant the patent. We conclude, therefore, that while the claim as issued is limited to the crystalline form of cefadroxil exhibiting the specified x-ray diffraction pattern, it is not limited to the compound in its pre-ingested form with the manufacturing characteristics which Bristol emphasized during prosecution.[4]

2.

We turn next to the question of whether Bouzard monohydrate is actually found in the stomach of patients who ingest cefadroxil DC. One answer is that no one knows—the scientific fact appears to be that there is no known way to actually sample the contents of patients' stomachs at the precise moment and conduct the x-ray diffraction analyses required to ascertain if all 37 lines described in the patent are present.

For its proof Bristol offered instead the testimony of its principal scientific witness, Dr. Harry Brittain, who described various studies and experiments simulating the environment of the human stomach which were conducted under his auspices; Zenith countered with the testimony of its principal scientific witness, Dr. Martha Greenblatt. The trial judge, after hearing all the evidence, concluded

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[4] The trial court apparently reached the same conclusion: "use of converted Bouzard monohydrate by a patient who ingests cefadroxil DC is an infringing use." (But see note 6 regarding the significance of the term 'use.')

that the Bouzard monohydrate in fact does inevitably form in the patient's stomach after ingestion of cefadroxil DC. In deciding this issue, the court specifically resolved the conflicting testimony presented by Dr. Brittain and Dr. Greenblatt:

> [T]he Court finds that Brittain has established by a preponderance of evidence, well within his range of expertise, that cefadroxil DC in fact converts *in vivo* to Bouzard monohydrate.
>
> The strength of Brittain's experiments and results is their totality. Piece by piece, Brittain built an impressive collection of data. The results of each series of experiments strengthen the results of each other set of experimental results. The total effect of the experiments is to prove with sufficient certainty the fact of conversion *in vivo*.
>
> * * * *
>
> [A]lthough she may have significant expertise in fields of inquiry unrelated to the issues in this case, Greenblatt demonstrated little understanding of the problem at issue in this case or the reason for her procedures and thus played no role in the design of her experiments, . . ., was lax in her methodology, particularly in the recording of her procedures and observations, and in fact did not even participate in the second series of experiments. The Court finds that Brittain's . . . results are simply better supported and vastly more credible. According, those findings are adopted by the Court.
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> *Zenith II*, 24 USPQ2d at 1664, 1668.

Courts of law are not the optimal fora for trying questions of scientific truth; even less are appellate courts equipped to choose among conflicting scientific theories. Judges are dependent on the quality and strength of the scientific evidence brought before them. The trial judge who hears the witnesses and does the initial assessment of

the evidence deserves considerable latitude in eventually choosing sides based on what is ultimately an educated guess—that is what judging is about.

However, in determining whether a claim in a patent has been infringed, the scientific theories utilized must establish the presence of the limitations recited in the claim. In this case, Dr. Brittain based his scientific conclusions on three kinds of tests—visual observation (obtained through optical microscopy), birefringence comparison, and x-ray diffraction pattern comparison. The trial judge explained:

> Brittain first established indisputably through photomicrography that cefadroxil DC crystals are much smaller than Bouzard monohydrate crystals, and are much different in shape. He also established that cefadroxil DC crystals exhibit a much weaker birefringence than do crystals of Bouzard monohydrate, which are highly birefringent. Thus, through microscopy, Brittain could determine with a high degree of certainty whether a sample of wetted cefadroxil DC had changed its crystalline form, and could conclude to a lesser extent that the form to which it had changed was Bouzard monohydrate. Although changes in the physical properties of shape, size and birefringence of the cefadroxil DC crystals could be conclusively determined through microscopy, *Brittain could not determine by observation alone that the larger, more birefringent crystals were necessarily Bouzard.* To determine conversion to Bouzard with great certainty, Brittain ran x-ray powder diffraction patterns, a technique that in essence takes the "fingerprint" of a crystalline compound. *Through x-ray diffraction analysis, Brittain determined with much greater confidence that all of the conversions suspected after optical examination had in fact been to Bouzard monohydrate.* (Emphasis added).
>
> *Id.* at 1665.

The key piece of evidence, then, was the x-ray diffraction pattern analysis. This is also what the claim in the patent requires. The first two kinds of tests are only inferentially relevant given that the claim is drafted in terms of x-ray diffraction lines. Thus they cannot substitute for a proper comparison of those lines.

And here a major problem arises. In order to establish its case, Bristol had to show that the accused compound infringed the claim contained in the patent.[5] This required Bristol to show that the diffraction pattern of cefadroxil DC following its conversion *in vivo* displayed the same diffraction pattern as that of the claimed compound. The district court, instead of requiring the comparison of the accused compound following conversion to be made with the lines specified in the claim, allowed Bristol to make the comparison with the diffraction pattern exhibited by a sample (the reference pattern) of a material considered by Bristol to be the patented compound.

As we have repeatedly said, it is error for a court to compare in its infringement analysis the accused product or process with the patentee's commercial embodiment or other version of the product or process; the only proper comparison is with the claims of the patent. *E.g., Martin v. Barber*, 755 F.2d 1564, 1567, 225 USPQ2d 233, 235 (Fed. Cir. 1985).

The difficulty was compounded. The x-ray diffraction pattern exhibited by Bristol's sample (the reference pattern) consisted of a table of only 30 lines of relative intensities. Of this total, the court only compared 22 lines to corresponding lines recited in the claim. *Zenith II*, 24 USPQ2d at 1665. Based on its comparison, the court concluded the two were sufficiently similar to per-

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[5] A finding that a claim is infringed is a necessary prerequisite to a finding that there has been an act constituting inducement to infringe under § 271(b). *See Met-Coil Sys. Corp. v. Korners Unlimited, Inc.*, 803 F.2d 684, 687, 231 USPQ 474, 477 (Fed. Cir. 1986).

mit Bristol to use the reference pattern in its infringement analysis. In fact, the number of lines recited in the claim is 37. Thus, 15 of the lines recited in the claim (representing about 40% of the total) were not considered by the court in its comparison. Although the term "essentially" recited in the claim permits some leeway in the exactness of the comparison with the specified 37 lines of the claim, it does not permit ignoring a substantial number of lines altogether. It is the claim that sets the metes and bounds of the invention entitled to the protection of the patent system.

On the basis of this evidence the trial court concluded that when cefadroxil DC is ingested Bouzard monohydrate is created in a patient's stomach, that that constitutes an infringing use, and that therefore the sale of cefadroxil DC by Zenith would constitute inducement of infringement under 35 U.S.C. § 271(b). Since the finding of infringement was based on testimony which incorporated an improper comparison, and since that comparison was an essential element in the conclusion that infringement occurred, the conclusion that Zenith by selling cefadroxil DC would engage in inducement of infringement is insupportable. Zenith is correct that there was a failure of proof as to whether any crystals, assumed to form in the stomach from ingested cefadroxil DC, literally infringe the '657 claim. In the absence of evidence comparing the '657 claim with the cefadroxil DC after ingestion Bristol has failed to establish any infringing use and therefore we must reverse the district court's conclusion that Zenith's sale of cefadroxil DC induces infringement of the '657 patent.[6]

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[6] As noted previously, Zenith offered three other grounds on which the judgment of the trial court could be reversed: an incidental conversion to Bouzard crystals does not "use" the claimed compound; the reverse doctrine of equivalents forecloses literal infringement by conversion; and equitable estoppel. In view of our disposition of the appeal we need not address these other grounds for reversal.

3.

On the question of infringement under the doctrine of equivalents, the trial court decided for Zenith, finding that Bristol, through statements it made during the '657 prosecution, was estopped via prosecution history estoppel from asserting that cefadroxil DC infringed under the doctrine of equivalents. According to Bristol, this was error, because the statements relied on by the district court do not support a finding that there was an estoppel; thus the doctrine of equivalents, properly applied, provides an alternative ground on which the judgment for Bristol could be affirmed.

Bristol's point has merit. The essence of prosecution history estoppel is that a patentee should not be able to obtain, through litigation, coverage of subject matter relinquished during prosecution. *See Loctite Corp. v. Ultraseal Ltd.*, 781 F.2d 861, 870, 228 USPQ 90, 96 (Fed. Cir. 1985). The legal standard for determining what subject matter was relinquished is an objective one, measured from the vantage point of what a competitor was reasonably entitled to conclude, from the prosecution history, that the applicant gave up to procure issuance of the patent. *See Prodyne Enters., Inc. v. Julie Pomerantz, Inc.*, 743 F.2d 1581, 1583, 223 USPQ 477, 478 (Fed. Cir. 1984); *Kinzenbaw v. Deere & Co.*, 741 F.2d 383, 389, 222 USPQ 929, 933 (Fed. Cir. 1984), *cert. denied*, 470 U.S. 1004 (1985). Here, we do not believe a competitor would have been reasonably justified in concluding that Bristol, through the statements in question, gave up coverage of those forms of Bouzard monohydrate other than the pre-ingested form.

There is nothing in the record indicating that the statements about manufacturing benefits played any role in the procurement of the '657 patent. As noted earlier, in these statements Bristol argued the superior manufacturing-related characteristics exhibited by Bouzard monohydrate *in relation to prior forms of cefadroxil.* Yet, these prior

forms of cefadroxil were never asserted as prior art by the examiner, and the examiner expressly indicated that Bristol's assertions were not a factor in determining patentability. Moreover, according to the examiner's statement of reasons for allowance, the sole basis upon which allowance was challenged, and upon which the '657 patent was eventually issued, was related to a single prior art reference, Garbrecht, U.S. Patent No. 3,781,282,[7] and Bristol's successful showing that the claimed compound was not inherent in that reference. There is no indication the examiner ever relied on the statements regarding manufacturing-related characteristics in allowing the patent to issue.[8]

Zenith asserts that the statements in question forestalled an obviousness rejection of the claim on the basis of the prior forms of cefadroxil. That, however, is at best highly speculative; it is unpersuasive in view of the examiner's statement of reasons for allowance. Thus, the

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[7] According to MPEP § 1302.14:

> One of the primary purposes of [a statement of reasons for allowance] is to improve the quality and reliability of issued patents by providing a complete file history which should clearly reflect, as much as is reasonably possible, the reasons why the application was allowed. Such information facilitates evaluation of the scope and strength of a patent by the patentee and the public and may help avoid or simplify litigation of a patent.

The absence of any reference to the manufacturing related characteristics in the statement of reasons for allowance supports our conclusion that the examiner did not rely on such characteristics in issuing the patent.

[8] Although actual reliance by the examiner need not be shown, if an estoppel is to rest upon argument made during the examination process, the circumstances must be such as to permit the inference that such reliance in fact occurred. A showing that the conduct in question played a material role in the issuance of the patent usually suffices. *See Mannesmann Demag Corp. v. Engineered Metal Prod.*, 793 F.2d 1279, 1285, 230 USPQ2d 45, 48 (Fed. Cir. 1986).

court's conclusion, that the statements in question gave rise to prosecution history estoppel, is insupportable.

However, any error in the court's application of prosecution history estoppel was harmless; the court's conclusion that the doctrine of equivalents is inapplicable to this case is correct as a matter of law. To prove infringement under the doctrine of equivalents, Bristol bore the burden of showing that cefadroxil DC was the equivalent of Bouzard monohydrate. *See Corning Glass Works v. Sumitomo Elec., U.S.A., Inc.*, 868 F.2d 1251, 1259, 9 USPQ2d 1962, 1967 (Fed. Cir. 1989). A necessary part of the function/way/result equivalency analysis is the *function* of the substituted element as seen in the context of the patent, the prosecution history, and the prior art. *Graver Tank & Mfg. Co. v. Linde Air Products Co.*, 339 U.S. 605, 609 (1950), *reh'g denied*, 340 U.S. 845 (1950).

In view of Bristol's numerous statements in the prosecution history regarding the superior manufacturing-related benefits of the Bouzard crystal in relation to the prior forms of cefadroxil, it is clear that the primary, if not the only, function of the Bouzard crystal form of the drug as compared to other forms is to facilitate pre-ingestion manufacturing. No other intended function is described or suggested.[9] Since any unanticipated production of the Bouzard crystal in the patient's stomach as a result of ingesting cefadroxil DC does not even remotely perform that function, the "function" part of the function/way/result test of equivalency is not met. As a matter of law, there can be no infringement under the doctrine of equivalents.

Bristol cites a number of cases to demonstrate that the doctrine of equivalents has been applied to find infringe-

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[9] It is self-evident that the function cannot be described more broadly, i.e. as the delivery of therapeutic value to the patient, for that is the function attributable to cefadroxil *per se*, which is prior art in relation to Bouzard monohydrate.

ment in situations involving *in situ* or *in vivo* conversions. However, these cases do not support Bristol's argument. In two, *Broadview Chemical Corp. v. Loctite Corp.*, 159 USPQ 80 (D. Conn. 1968), *aff'd in relevant part*, 406 F.2d 538, 160 USPQ 449 (2d Cir.), *cert. denied*, 394 U.S. 976 (1969) and *Studiengesellschaft Kohle, M.b.H. v. Dart Industries, Inc.*, 549 F. Supp. 716, 216 USPQ 381 (D.Del. 1982), *aff'd*, 726 F.2d 724, 220 USPQ 841 (Fed. Cir. 1984), the doctrine of equivalents was not the issue in the case.[10] In the others, *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 588 F. Supp. 1455, 221 USPQ 426 (N.D. Tex. 1983, *aff'd*, 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984); *Chemical Cleaning Corp. v. Dow Chemical Co.*, 379 F.2d 294, 155 USPQ 49 (5th Cir. 1967), *cert. denied*, 389 U.S. 1040 (1968); *Ortho Pharmaceutical Corp. v. Smith*, 18 USPQ2d 1977 (E.D. Pa. 1990), *aff'd*, 959 F.2d 936, 22 USPQ2d 1119 (Fed. Cir. 1992); and *Beecham Group Ltd. v. Bristol Lab. Ltd.*, [1978] R.P.C. 153 (House of Lords 1977), the substituted compound or ingredient converted *in vivo* or *in situ* to the compound or ingredient called for by the claim, and performed the same function as that of the claim.[11] The infringer was thus using the equivalent ele-

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[10] In *Broadview*, the claimed ingredient was found to be present in the accused product independently of the purportedly substituted ingredient. 406 F.2d at 541-42, 160 USPQ at 451. Thus, that product literally infringed. Equivalence between the two ingredients was not an issue in the case. In *Studiengesellschaft*, although it was unclear whether the trial judge had made findings on the doctrine of equivalents issue, we concluded on appeal that any such findings were inappropriate and unnecessary insofar as the court's judgement was sustainable on the basis of literal infringement. 726 F.2d at 728, 220 USPQ at 843.

[11] In *Atlas Powder*, it was found that the substituted compound—an oil-in-water emulsifier—converted *in situ* to the claimed compound—a water-in-oil emulsifier—which in turn performed its intended function—forming an emulsion between oil and water. 588 F. Supp. at 1472, 221 USPQ at 440, *aff'd*, 750 F.2d at 1581, 224 USPQ at 417. In *Chemical Cleaning*, it was determined that the substituted compound—monomethylolthiourea—disassociated in op-

ment to perform the same function as the claimed compound, a typical case for doctrine of equivalents application.

Even assuming that cefadroxil DC converts *in vivo* to Bouzard monohydrate in measurable amounts, that particular crystalline form does not perform the function of facilitating encapsulation. On the record before us, the trial court was correct in his judgment that Bristol had failed to establish infringement under the doctrine of equivalents.

CONCLUSION

For the reasons given, the judgment of the trial court in favor of Bristol on count one is reversed.

REVERSED

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eration to form the claimed compound—thiourea—which in turn performed its intended function—acting as a sequestering agent for copper. 379 F.2d at 296, 155 USPQ at 49. In *Ortho*, it was found that the substituted compound—norgestimate—converted *in vivo* to the claimed compounds—norgestral and norgestral acetate—which in turn performed their intended function—contraception. 18 USPQ2d at 1985-86, *aff'd*, 959 F.2d at 939, 22 USPQ2d at 1122. Finally, in *Beecham*, it was determined that the substituted compound—hetacillin—converted *in vivo* to the claimed compound—ampicillin—which in turn performed its intended function —acting as an antibiotic. [1978] R.P.C. at 167, 182-83, 202.

APPENDIX B

DISTRICT COURT
D. NEW JERSEY

No. 91-3423

ZENITH LABORATORIES INC.

v.

BRISTOL-MYERS SQUIBB CO.

Decided July 21, 1992

Wolin, J.

Bristol-Myers Squibb Company ("Bristol"), a Delaware corporation, is the owner of United States Patent No. 4,504,657 ("the '657 patent"), issued on March 12, 1985. The '657 patent includes a single claim for a specific crystalline form of cefadroxil monohydrate (hereinafter "Bouzard monohydrate").[1] Cefadroxil is a cephalosporin antibiotic compound that has a number of medical uses. Bristol previously owned the now-expired

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[1] The patent claim reads:

We claim:

1. Crystalline 7-[D-α-amino-α- (p- hydroxypheny) l- acetamido] -3-methyl-3 -cephem-4- carboxylic acid monohydrate exhibiting essentially the following x-ray diffraction properties: [followed by a table of numbers corresponding to the x-ray diffraction characteristics of the Bouzard monohydrate]

(United States Patent No. 4,504,657 at page 18, lines 65-69).

United States Patent No. 3,489,752, which issued on January 13, 1970 and claimed all forms of cefadroxil.

This action was filed by Zenith Laboratories, Inc. ("Zenith"), a New Jersey corporation, against Bristol on August 5, 1991. Among other claims for relief, Zenith seeks a declaration that "cefadroxil DC", a hemihydrate form of cefadroxil for which Zenith has obtained Food and Drug Administration ("FDA") approval to market in finished dosage form as a generic equivalent of cefadroxil monohydrate, does not infringe the '657 patent.[2] Although Bristol does not contend that cefadroxil DC infringes the '657 patent in its manufactured, pre-ingested state, it does contend that after ingestion, the drug "converts" to the Bouzard monohydrate inside the body, or *"in vivo,"* and that such conversion renders cefadroxil DC an infringing compound under the doctrine of equivalents, or alternatively, that sales of cefadroxil DC by Zenith would constitute inducement of infringement of the '657 patent.

In an Opinion dated February 21, 1992, the Court granted summary judgment in Zenith's favor on the issue of *in vivo* conversion, and found that Zenith was entitled to a declaration that cefadroxil DC does not infringe the '657 patent. An Order reflecting this ruling was filed on March 4, 1992. On motion for reconsideration, in an Opinion and Order dated April 13, 1992, the Court vacated its March 4, 1992 Order, motivated in substantial part by the uncommon manner and speed by which the record was created for the motion, and by how early in the proceedings the motion was brought. Recognizing the immediacy of the rights at stake, the Court set down the issue of infringement for trial on an accelerated basis following expedited discovery.

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[2] A hemihydrate is a crystal form containing two molecules of water for each molecule of a chemical compound. A monohydrate contains one water molecule for each molecule of the chemical compound.

The issue of infringement was tried to the Court between May 26, 1992 and June 5, 1992, during which six days of evidence was received. The primary factual issue at trial was whether cefadroxil DC converted *in vivo* to the Bouzard monohydrate. Set forth below is a summary of the testimony at trial, and the Court's findings of fact and conclusions of law as required by Federal Rule of Civil Procedure 52(a). Based on these findings and conclusions, a judgment will be entered in Bristol's favor.

I. *THE EVIDENCE AT TRIAL*

The evidence at trial consisted for the most part of expert testimony presented by both parties. Both parties' experts conducted a number of experiments to investigate whether cefadroxil DC converts *in vivo* to the Bouzard monohydrate. These experts were presented as witnesses to explain their theories of conversion, experimental methodologies, test results, and conclusions based on those results. Additional experts were presented to provide foundations for assumptions made by some of the experts who conducted experimental studies, or to rebut the assumptions, methodologies, theories, or conclusions of other expert witnesses. The Court will summarize each party's case in the order presented at trial.

A. *Zenith's Direct Case*

C. David Smith

Zenith's first witness was C. David Smith, its vice-president of quality assurance. Mr. Smith testified as to the status of Zenith's FDA application, and as to the formulation for Zenith's cefadroxil DC capsules. He testified that the capsules contain, in addition to the cefadroxil material, lactose, sodium starch glycolate and magnesium stearate. (Tr. 17)[3] These nonactive ingredients, known as "excipients", are included in the capsules for different purposes. Lactose is used as a filler. Sodium starch

[3] "Tr. ———" refers to the trial transcript at the page indicated.

glycolate swells greatly when exposed to water, and is included as a disintegrant to break apart the capsule. (Tr. 18) Magnesium stearate is a lubricant useful in machining the capsules. (*Id.*)

Edwin C. Rothstein

Zenith next presented the testimony of Edwin C. Rothstein, president of Leberco Testing, Inc. ("Leberco"), an independent testing laboratory located in New Jersey. Leberco was retained by Zenith to perform dissolution and solubility tests on cefadroxil DC and the Bouzard monohydrate, both in their formulated and bulk forms.

1. *Dissolution Tests*

Rothstein testified that Leberco technicians conducted dissolution tests in which they recorded the rates at which 500 milligram capsules of cefadroxil DC and Bouzard monohydrate dissolved into simulated gastric juice. (Tr. 39) The tests were performed by placing 500 milligram capsules in a dissolution basket rotated at 100 revolutions per minute ("rpm") in 900 milligrams of simulated gastric juice without enzymes. (PX 21)[4] The percentage of material dissolved into the dissolution media was measured and recorded at intervals of 3, 5, 7.5, 10 and 20 minutes. (*Id.*) Six runs were performed and averaged on each substance. From the results of this experiment, Rothstein concluded that between three and five minutes, cefadroxil DC had a higher dissolution rate than the Bouzard monohydrate. (Tr. 40) He also concluded that cefadroxil DC had a higher total solubility than Bouzard monohydrate. (*Id.*) The same tests were run using 1000 milligram tablets. (*Id.*) Rothstein concluded that the results of this experiment were essentially the same as with the first test. (Tr. 40-41; PX 22)

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[4] "PX ———" refers to plaintiff's exhibit numbered as indicated. Likewise, "DX ———" refers to the indicated defendant's exhibit.

Rothstein testified that Leberco performed an additional experiment designed to determine whether the dissolution rates observed were affected in any way by any difference between the Zenith gelatin capsule and the Bristol gelatin capsule. The experiment consisted of comparing the dissolution rate of 350 milligrams of cefadroxil DC in a Zenith capsule with the dissolution rate of 350 milligrams of cefadroxil DC in a Bristol capsule. (PX 23) From the measured results of this test, Rothstein concluded that the gelatin capsule shell had no effect on the dissolution rates of the two cefadroxil materials. (Tr. 41)

One further dissolution experiment was conducted by Leberco. A comparison was made of the dissolution of capsules of cefadroxil DC and Bouzard monohydrate in 30 milliliters of simulated gastric juice at 37° C in a dissolution basket rotated at three rpm. (PX 24) Rothstein testified that the dissolution test could not be performed due to the small quantity of fluid used. (Tr. 42) Therefore, only visual observations could be made. (*Id.*) Rothstein testified that after three minutes, the Zenith capsule had released most of its contents, but that the Bristol capsule still contained most of its contents. (*Id.*)

2. *Solubility and Bulk Density Tests*

Rothstein testified that Leberco technicians performed solubility tests on cefadroxil DC and Bouzard monohydrate. Solubility is a measure of the quantity of a given material that can be dissolved in a given solvent at a given temperature and pressure in a given volume. (Tr. 46) Rothstein testified that five grams of a material was placed in 100 milliliters of deionized water that was maintained at a specific temperature and intermittently agitated for ten hours. Undissolved materials were then filtered, and the clear filtrate was then spectrophotometrically analyzed to determine its cefadroxil content. (*Id.*) This was done for each cefadroxil material at three temperatures: 4°C,

room temperature (between 23°C and 25°C) and 50°C. (*Id.*) From the test results obtained (see PX 25, 26), Rothstein concluded cefadroxil DC is "clearly more soluble" than the Bouzard monohydrate under the conditions utilized. (Tr. 43)

Leberco also measured the bulk densities of cefadroxil DC and Bouzard monohydrate. (PX 25) From the tests, Rothstein concluded that cefadroxil DC has a bulk density considerably lower than that of Bouzard monohydrate.

Dr. Martha Greenblatt

The testimony of Dr. Martha Greenblatt was offered into evidence on Zenith's direct case through deposition transcript. Greenblatt was deposed by Zenith *de bene esse* on May 21, 1992. The transcript was accepted into evidence without objection. On Zenith's rebuttal case, Greenblatt testified in court.

Greenblatt is a professor at Rutgers University in New Jersey who teaches solid state chemistry, and is an expert in x-ray crystallography. (Deposition Tr. 5) She was asked to perform an experiment that was intended to determine whether, at the time a capsule of cefadroxil DC bursts in simulated gastric acid, cefadroxil DC has already converted to Bouzard monohydrate. This was accomplished by Greenblatt placing a Zenith capsule in simulated gastric acid until the capsule breached, and at the moment that cefadroxil began to pour out of the capsule, she froze the material in liquid nitrogen. (Dep. 11) This experiment was repeated. She then freeze-dried the frozen samples, and recorded the x-ray powder diffraction patterns of two samples. (Dep. 15-16; PX 31)

In the first experiment, Greenblatt placed a Zenith capsule in a dissolution basket that was then immersed in 100 milliliters of simulated gastric acid maintained at 37°C and rotated at six rpm. At one minute, 54 seconds, Greenblatt observed that the capsule had burst, and re-

moved the basket from the beaker and placed it into the liquid nitrogen within five seconds. A second experiment was performed in which Greenblatt observed a burst in the capsule at approximately two minutes. Both frozen-samples were placed in a freeze-drier overnight.

The next day, 20 hours after the samples were frozen (Tr. 894), x-ray diffraction patterns of the samples were recorded and designated Z1 and Z2. (PX 31) These patterns were compared to "standard" patterns made from samples of cefadroxil DC and Bristol's Bouzard monohydrate.[5] According to Greenblatt, the patterns for Z1 and Z2 were "identical" to the standard cefadroxil DC pattern. (Dep. 17) From the comparison, Greenblatt concluded that the cefadroxil DC samples she placed in acid and freeze-dried had not undergone any structural change in their crystal form. (Dep. 22)

Dr. Ralph R. Pfeiffer

Dr. Pfeiffer is a consultant at Purdue School of Pharmacy in the solid state drug chemistry group. (Tr. 65) He also does consulting and teaches seminars on polymorph formation and solvate formation, most recently for the F.D.A. (Tr. 66) He has extensive experience, including 30 years at Eli Lilly Company, in x-ray powder diffraction analysis, in the identification of polymorphs and solvates of drugs, and in other areas related to crystal formation and behavior. (Tr. 66) Pfeiffer was offered as an expert in x-ray powder diffraction analysis, crystal theory and the behavior of oral drug dosages in the human body.

Pfeiffer testified as to his comparison of x-ray diffraction patterns of cefadroxil DC and a prior art form of cefadroxil known as "Gottstein" cefadroxil. (Tr. 71-2) For the Gottstein pattern, Pfeiffer relied on the pattern attached to the declaration of Timothy Marr, which was

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[5] Greenblatt verified that the patterns obtained from bulk cefadroxil DC and formulated DC with excipients were identical.

filed with the United States Patent and Trademark Office in 1982. (Tr. 71; PX 33) Zenith also offered the declaration of David Whitehead, which was also filed with the United States Patent and Trademark Office, in which Whitehead declared that the Gottstein material utilized by Mar had not changed in the eleven years since it was first prepared. (PX 37) Pfeiffer used one of Dr. Greenblatt's patterns as representative of cefadroxil DC. (Tr. 71) He concluded, after comparing the patterns, that cefadroxil DC and Gottstein cefadroxil "are of the same crystal structure." (Tr. 72) Based on this conclusion, Pfeiffer also concluded that the structure-dependent properties of both materials—including equilibrium solubility, melting point and density—would be the same. (Tr. 82-83) Pfeiffer further opined that if one material converted to the Bouzard monohydrate when exposed to an aqueous environment, so would the other. (Tr. 83)

Dr. Pfeiffer testified that in his opinion, it was unlikely that cefadroxil DC could convert *in vivo* to the Bouzard monohydrate. (Tr. 83-84) He believed that a number of conditions existed in the stomach that would preclude the dissolution and recrystallization processes that would be required for conversion. (Tr. 84) Specifically, he believed that cefadroxil DC would dissolve very quickly in the stomach and prevent the creation of a super-saturated environment needed for recrystallization. (Tr. 88-89) In addition, Pfeiffer believed that the mixing action of the stomach would tend to disperse any super-saturated region that might otherwise form. (Tr. 89)

Dr. Pfeiffer testified further as to the conditions that he believed were necessary for conversion to occur. In addition to the super-saturated solution, he testified that nucleation must occur. (Tr. 89) Conditions that could produce nucleation include evaporation, cooling of the solution, and inducement of mechanical stress. (Tr. 90) Recrystallization could also occur if nuclei were already present. (Tr. 90) Pfeiffer opined that none of these conditions are present in the stomach. (Tr. 91)

Pfeiffer testified as to the conclusions that he drew from the tests performed by Leberco, introduced through Dr. Rothstein. He concluded from the results of the equilibrium solubility tests performed by Leberco that cefadroxil DC did not convert to Bouzard monohydrate because at the end of ten hours in simulated gastric acid, different amounts of the two material dissolved into identical volumes of the fluid. To Pfeiffer, this indicated that no conversion occurred because if it had, equal amounts of material would have dissolved. (Tr. 92) This is true even though, in their dissolved states, cefadroxil DC and Bouzard monohydrate are identical—they are simply the compound cefadroxil. (Tr. 92)

On one last topic, Pfeiffer opined that Dr. Greenblatt's experiments minimized the chance that changes would occur in cefadroxil DC after it had been removed from the dissolution medium. (Tr. 93) He further agreed with her conclusion that no conversion had occurred. (Tr. 93)

B. *Bristol's Case*

Dr. Howard Goldin

Bristol's first witness, Dr. Goldin, is a Board-certified doctor of internal medicine and gastroenterology. (Tr. 246) He was offered as an expert on the conditions that exist inside the human stomach. Goldin was asked to provide a protocol for simulating stomach conditions, which could be used in *in vitro* experiments intended to determine whether cefadroxil DC converted *in vivo* to the Bouzard monohydrate. (Tr. 253) According to Goldin, ethical constraints precluded actual *in vivo* experiments from being conducted for this purpose. (Tr. 253)

The protocol provided by Goldin consisted of the use of 30 milliliters of actual gastric juice maintained at body temperature (37°C) and gently agitated at three rpm. (Tr. 254, 264) Goldin also recommended that simulated gastric juice (a 0.1 solution of hydrochloric acid) could be

used. (Tr. 255) The stirring rate was chosen as an approximation of the agitation that occurs in the stomach. Goldin testified that for the most part, the stomach is in a flaccid state, with only intermittent gentle waves that "barely agitate the contents of the stomach." (Tr. 265) For only approximately five out of every 90 to 120 minutes are there vigorous contractions in the stomach. (Tr. 265) An *in vitro* stirring rate of 100 rpm, in Dr. Goldin's opinion "far exceed[s] the physiologic spectrum of the human stomach." (Tr. 270)

Samples of actual gastric juice provided to Bristol for experimentation uses by Dr. Goldin were obtained from Goldin's patients during a routine suction of the contents in preparation for an endoscopic examination. (Tr. 265-66) The patients had all fasted prior to the examination. (Tr. 265) Most of the gastric acid obtained had a pH of between one and two. (Tr. 266) The average volume of acid suctioned from the patients was 30 milliliters. (Tr. 267) Essentially all of a stomach's contents are removed by the suctioning. (Tr. 267) The pH of gastric acid in a non-fasting patient is generally higher (less acidic) due to neutralization by the ingested solids or liquids. (Tr. 266)

Goldin opined that experiments utilizing his specified conditions would simulate *in vivo* conditions. (Tr. 270) He further opined that he did not believe that much of a difference would be observed if gastric acid from non-fasting patients were used, even if it consisted of a greater volume of fluid. (Tr. 274-75) Goldin opined that a volume of gastric acid between 30 and 240 milliliters was within the physiologic range of the human stomach. (Tr. 278) He also opined that a stirring rate between three and ten rpm would also be within that range, but that 25 rpm would fall outside of the range. (Tr. 281-82)

Goldin ultimately concluded that he would expect conversion to occur *in vivo* if it occurred *in vitro* under the conditions that he specified. (Tr. 284-85)

Dr. Robert J. Levine

The testimony of Dr. Levine was offered into evidence by Bristol through deposition transcript. Levine was deposed by Bristol *de bene esse* on May 11, 1992. The transcript was accepted into evidence without objection as defendant's exhibit 20. (Tr. 317-18)

Levine is a professor of medicine at Yale University School of Medicine in Connecticut, specializing in medical ethics. (Dep. 5) His previous experience included serving as chief of the clinical pharmacology section at Yale University School of Medicine. (Dep. 11) He has reviewed more than 5,600 proposals to do medical research on human subjects. (Dep. 13) In Levine's opinion, no institutional review board would approve research on human subjects solely to defend a patent. (Dep. 14-15) He further opined that he did not believe that an *in vivo* experiment could be designed to test whether cefadroxil DC converts to Bouzard monohydrate that would not be subject to the same criticisms to which the *in vitro* experiments have been subjected. (Dep. 15)

Dr. Gerond V. Lake-Bakaar

Dr. Lake-Bakaar is a physician who, like Dr. Goldin, specializes in internal medicine and gastroenterology. (Tr. 318-19) He teaches medicine at the State University of New York at Stony Brook. (Tr. 319) Bristol offered Lake-Bakaar as an expert in gastroenterology. (Tr. 320)

Lake-Bakaar testified that he conducts research in gastroenterology and has on a number of occasions designed *in vitro* studies that were intended to simulate *in vivo* conditions, (Tr. 320, 326), and that such tests are frequently relied on by gastroenterologists to predict *in vivo* results, (Tr. 327). In his opinion, the *in vitro* conditions employed by Dr. Harry Brittain, a witness for Bristol discussed *infra,* of 30 milliliters of 0.1 N HCl maintained at 37°C with gentle agitation, closely simulates conditions

in the human stomach. (Tr. 332-33) In his experience, Dr. Lake-Bakaar has encountered varying volumes of gastric acid in patients, ranging between 20 and 80 milliliters. (Tr. 333) He also opined that mixing rates between three rpm and 100 rpm covered a range that exceeded the range of agitation that he believes occurs in the human stomach. (Tr. 336) In his opinion, 10 rpm is the average rate of mixing in the human stomach, to the extent it can be quantified in those terms. (Tr. 336, 369-70) Lake-Bakaar further opined that little difference exists between the gastric juice of fasted and non-fasted patients. (Tr. 337)

Dr. Lake-Bakaar testified that, in his opinion, Dr. Brittain's failure to account for emptying and replenishment of stomach juices does not affect the validity of his simulations, because the emptying rate of the human stomach is sufficiently slow such that it would be minimal over the short time interval that elapsed before Brittain observed conversion in his experiments. (Tr. 334-35). Lake-Bakaar estimated that in five minutes, the human stomach replaces approximately five percent of its gastric acid. (Tr. 334). This rate remains constant without regard to whether additional fluid has been ingested. (Tr. 358-59)

He further opined that Brittain's failure to take into account absorption of materials through the stomach wall did not affect the validity of his simulation, because, with the exception of extremely acidic compounds, such absorption is minimal. (Tr. 335) He also testified that he did not believe "sink" conditions existed in the human stomach. (Tr. 337) In his understanding, "sink" conditions exist when the concentration of a solvent is altered by, for example, emptying and replacement. (Tr. 337-38)

For his final conclusion, Lake-Bakaar opined that, if conversion actually occurs under the range of conditions observed by Dr. Brittain in his *in vitro* experiments, he believes that conversion would also occur *in vivo*. (Tr. 339-40)

Dr. Harry G. Brittain

Dr. Brittain has a doctorate in chemistry, has done extensive post-doctoral fellowship work, taught chemistry at several colleges, and has, since 1985, worked for Bristol or one [of] its predecessor corporations. Brittain was offered as an expert in physical-chemistry, x-ray powder diffraction analysis and optical microscopy. (Tr. 384) As part of his job responsibilities at Bristol, Dr. Brittain examines, compares and analyzes x-ray powder diffraction patterns on a regular basis. (Tr. 630-31) Relying on the conditions specified by Drs. Goldin and Lake-Bakaar, Dr. Brittain conducted numerous experiments that were designed to determine whether cefadroxil DC converts to Bouzard monohydrate *in vivo* after ingestion. He designed all of his own experiments. (Tr. 495) The conditions and results of these experiments are summarized in tables received into evidence as defendant's exhibits 42a-d.

1. *Brittain's Theory of the Conversion Mechanism*

Dr. Brittain testified that he believes conversion occurs because cefadroxil DC, when wetted, partially dissolves and forms a saturated layer around the undissolved material, and then recrystallizes as the Bouzard monohydrate. (Tr. 510) He opined that when liquid enters a cefadroxil DC capsule, a micro-environment of saturation is created that allows partial dissolution of cefadroxil DC crystals that act as nuclei for the formation of Bouzard monohydrate crystals. (Tr. 629, 806) He does not believe that the beaker in which he conducted his experiments had any effect on the conversion because he believes that conversion occurs inside of the capsule. (Tr. 510)

2. *Initial Experiments*

The first experiments undertaken by Brittain to investigate conversion are summarized in defendant's exhibit. By placing a range of weights of cefadroxil DC in a series of test tubes with one milliliter of water and observing in

which tubes all of the drug dissolved, Brittain determined that the equilibrium solubility of cefadroxil DC was approximately between 10.1 and 16.3 milligrams per milliliter. (Tr. 390; DX 17) This was considered consistent by Brittain with his understanding that cefadroxil DC has an equilibrium solubility of 12 milligrams per milliliter. (DX 17)

Brittain also observed that the fine cefadroxil DC powder that he placed in the test tubes turned granular in appearance after being in contact with the water for one minute. (Tr. 390; DX 17) Upon examination by optical microscope at 400 magnification, Brittain observed that the granular solids in the solution had a significantly different appearance from the unwetted cefadroxil DC. The initial cefadroxil DC consisted of small needle-shaped crystals, but the wetted cefadroxil consisted of much larger rhombic crystals. (Tr. 396-97; DX 17) The larger rhombic crystals are characteristics, in Brittain's opinion, of crystals of Bouzard monohydrate. (Tr. 400)

A significant difference was also observed between the birefringence of both samples. The wetted sample was significantly birefringent, but the unwetted sample was only slightly birefringent. (DX 17) The phenomenon of birefringence is the degree to which the indices of refraction in a given material scatters light passed through the material. By passing polarized light through a substance and then observing the substance through a second polarizer rotated 90° from the initial polarizer, the relative degree to which light is scattered as it passes through different substances can be observed as varying intensities of brightness. (Tr. 383) Birefringence can be a useful test for identifying crystals, or comparing whether two substances are the same crystal. (Tr. 383) If the same crystals are present, they will have the same birefringent characteristics. According to Brittain, the birefringence of cefadroxil DC is "extremely weak". (Tr. 401)

3. *Second Series of Experiments*

The next series of experiments performed by Dr. Brittain is summarized in defendant's exhibits 14 and 18, but is described in greater detail in Brittain's laboratory notebook, offered into evidence as defendant's exhibit 16. In that experiment, he initially photomicrographed dry cefadroxil DC to reconfirm its particle size and shape as small needles, and verified that it exhibited weak birefringence. (Tr. 405) He also ran an x-ray powder diffraction analysis of a sample of dry cefadroxil DC that he possessed, to obtain a diffraction pattern for use as a reference in his future experimentation. (Tr. 406-07) He also obtained an x-ray diffraction pattern for Bouzard monohydrate. (Tr. 410)

For this experiment, Brittain placed a dry 10 milligram sample of cefadroxil DC on a microscope slide, wetted it with water, and observed it under a microscope. (Tr. 411-12; DX 14) He observed that the cefadroxil material transformed from very small crystals to large block-like crystals. (Tr. 412) In a second experiment, Brittain placed 100 milligrams of cefadroxil DC on a slide, and wetted it with 0.1 N HC1 solution. (Tr. 413) He observed the same phenomena as in the prior experiment, except that the crystal faces appeared better formed, and the birefringence was more distinctive. (Tr. 413) The transformation of the crystals occurred within 30 seconds of being wetted. (DX 14) The sample remained in the solution for five minutes before it was removed and subjected to x-ray diffraction analysis. When the x-ray powder diffraction pattern obtained from the wetted cefadroxil DC was compared to the reference patterns, Brittain observed that the pattern for the wetted cefadroxil was equivalent to the reference pattern for Bouzard monohydrate. (Tr. 415)

A third experiment in this series was performed to determine whether cefadroxil DC converted to Bouzard monohydrate within a capsule immersed in fluid. In two separate runs, handfilled capsules of cefadroxil DC were

placed respectively in 250 milliliters of water and in 250 milliliters of 0.1 N HC1 solution and allowed to sit for respectively four and ten minutes, and were then removed, sliced open, and examined under the microscope for crystal shape and size, and for birefringence. (Tr. 416-18, 423; DX 16) These visual tests confirmed that the material had converted to Bouzard monohydrate. (*Id.*) X-ray diffraction analysis further confirmed that conversion had occurred. (Tr. 418, 424, 425)

4. *Dissolution Experiments*

In a series of dissolution experiments, Dr. Brittain utilized the *in vivo* conditions specified by Dr. Goldin, in an attempt to determine with more certainty whether conversion would occur in the human stomach. Those conditions consisted of 30 milliliters of simulated gastric juice maintained at 37°C and stirred at three rpm.

In the first experiment, approximately 300 milligrams of cefadroxil DC was placed in a clear capsule and lowered into a dissolution kettle that contained 30 milliliters of simulated gastric juice stirred at three rpm for a period of eight minutes. (Tr. 438) Optical microscopy was performed on the capsule, which revealed to Brittain, consistent with previous experiments, that the crystals had changed from small needles to large monohydrate crystals, and that the birefringence had also increased significantly. (Tr. 439) The same conditions were repeated and the same results were obtained. (Tr. 441-42) X-ray powder diffraction patterns were not run because the x-ray unit was not operating on that day. (Tr. 442)

Brittain later ran many other dissolution experiments, using varied condition of temperature, volume dissolution medium, and stirring rate. Tests were performed on handfilled capsules containing between 300 and 500 milligrams of cefadroxil DC, as well as on actual formulated Zenith cefadroxil DC 500 milligram capsules including excipients. Capsules were immersed in media

maintained at 37°C and at 25°C. Dissolution media volumes were varied between 30 and 900 milliliters. Both simulated gastric juice and actual gastric acid provided by Dr. Goldin were used as dissolution media, with pHs ranging between 1 and 6.5. Stirring rates were varied between zero and 100 rpm. Brittain testified at length during trial as to the conditions of these experiments. His laboratory notebook provides a contemporaneous record of the details of these experiments. (DX 16) The results of these experiments are summarized in table form in defendant's exhibits 42a-42c. For all of these experiments, similar tests were performed to reach uniform results. Optical microscopy observation of crystal size and birefringence, together with x-ray powder diffraction analyses, uniformly indicated to Dr. Brittain that conversion of cefadroxil DC to Bouzard monohydrate occurred under all of the varied experiment conditions. Brittain concluded that the pH of the dissolution medium had little or no effect on whether conversion would occur. (Tr. 533) He also concluded that the volume of the dissolution medium and stirring rate had little or no effect on whether conversion would occur. (Tr. 540-41)

5. *Protonation Experiment*

One of the claims raised by Zenith on motion for summary judgment was that cefadroxil DC wetted with acid could not recrystallize once dissolved, because the cefadroxil would become protonated as it reacted with the acid. Protonation occurs when a compound binds with free hydrogen ions as the acid reacts with the compound. (Tr. 468) To test this assertion, Brittain ran fourier transform infrared reflectance ("FTIR") analyses of the material he believed was converted cefadroxil and of unwetted Bouzard material, to obtain FTIR spectra. (Tr. 466-67) FTIR analysis is commonly used to determine whether a material has protonated. (Tr. 467) Brittain concluded from a comparison of the two spectra that the cefadroxil DC material had converted to the Bouzard monohydrate, and that it was not protonated. (Tr. 467)

6. *Light Scattering Experiments*

Although he did not believe that removing cefadroxil from the dissolution medium had any effect on the conversion process, Dr. Brittain designed a light-scattering experiment with which he could investigate whether conversion could be observed without removing a sample from the dissolution medium. (Tr. 548)

The apparatus used to conduct the light-scattering experiments consisted of a laser light source that was passed through a square cuvette containing three milliliters of liquid. (Tr. 550-52) On an adjacent side of the cuvette was a photomultiplier tube that received the light passing through the cuvette at a right angle to the laser source, and converted it to an electrical current that varied in proportion to the intensity of the scattered light. (Tr. 552) The electrical current was then converted to a voltage output that also varied in proportion to the scattered light intensity, which was amplified and displayed on an output device. (Tr. 552)

To isolate the laser light passing through the cuvette, and to minimize the effect of changes in ambient light levels, the laser light source was pulsed at a chosen frequency. Through use of a lock-in implifier, which amplified only the converted voltage signal with the same frequency as the pulsed laser source, the final displayed output, as recorded on a strip chart recorder, measured essentially just light that had originated from the laser light source. (Tr. 553) This apparatus was designed and built by Dr. Brittain.

To validate the system, Brittain mixed twenty milligrams of microcrystalline cellulose, a water insoluble substance, with water in a cuvette. (Tr. 554) The mixture was alternatively stirred with a magnetic stirrer, then allowed to settle, while the laser source passed through the cuvette. (Tr. 554-55) The output recorded on the

strip chart recorder showed changes in negative voltage that varied from a lesser negative voltage when the material was completely settled, to a maximum negative voltage when the stirring occurred. (Tr. 555) This indicated that the apparatus measured changes in the intensity of light scattered from the original laser source. (Tr. 555) When more particles are suspended in solution, more light is scattered.

Brittain then used the apparatus to determine whether changes in light could be detected as the cefadroxil DC was mixed in simulated gastric juice. To separate the possible effect on the test that dissolution, as opposed to conversion, would have on the light-scattering measurement, Brittain started with a filtered saturated solution of cefadroxil DC, because no further dissolution could occur if the saturated solution was held at a constant temperature. (Tr. 557) In the first series of runs, he added 25 milligrams of Bouzard monohydrate to the saturated solution, which was mixed vigorously while the scattered light intensity was measured by the light-scattering apparatus. (Tr. 558-59) Three strip chart traces were obtained in three separate runs, which revealed a fairly constant negative output. (Tr. 539) The materials in the cuvettes were examined by microscopy to verify that the Bouzard material was still present. (Tr. 561).

In the next series of runs of the experiment, Brittain replicated the conditions used in the first series, except that he used cefadroxil DC instead of Bouzard monohydrate. (Tr. 562) This experiment was also run and recorded three different times. (Tr. 563) The curves plotted in all three runs were essentially the same. (Tr. 568) They show a sharp arc-shaped decrease in negative voltage output through most of the first minute of the experiment, and then a gradual steady increase in negative voltage intensity through the remainder of the experiment. (DX 16, pages 148-49) Dr. Brittain believed that the initial decrease in intensity was due to dissolution of the cefadroxil DC crystals, which resulted in less scattering

of the laser signal because fewer solid particles were present to scatter the light. (Tr. 565) He also believed that the later increase in the scattered light intensity was consistent with conversion, because it indicated that some physical change had occurred in the tube at the approximate time that he had observed conversion in his other experiments. (Tr. 566-67, 569)

Another experiment was conducted in which Brittain used the same conditions of solution and stirring as used in the light-scattering experiment, but instead of measuring light intensity with the light scattering apparatus, he took a series of nine photomicrographs of material extracted out of the cuvette at different time intervals during a four minute period. (DX 16, pages 150-53) Birefringence was also examined. (Tr. 573) Brittain observed very small Bouzard crystals in the first photograph taken at 14 seconds. (Tr. 573) In each successive photograph, he observed larger and more crystals up until approximately two minutes, after which the appearance did not change significantly. (Tr. 575) From this, he concluded that evaporation did not play any role in conversion, because if the material converted only due to evaporation on the slide, each photograph would look the same. (Tr. 575) Brittain related these results to the light-scattering measurements by observing that the Bouzard crystals only began to aggregate at approximately one minute, the time at which the light scattering intensity began to increase. (Tr. 576) He opined that the aggregation of crystals at one minute was consistent with the change in light-scattering intensity that was observed beginning at that time interval. (Tr. 576)

Brittain conducted another series of light-scattering experiments in which he re-ran the first two series of experiments except that instead of using a saturated cefadroxil solution as the dissolution medium, he used only simulated gastric juice, in which he placed a greater quantity of cefadroxil material. (Tr. 577) This was done so that he could determine whether conversion occurred in an unsaturated solution. (Tr. 579-80)

When Brittain recorded the light scattering intensities of the Bouzard material, he plotted a different tracing from that obtained in the first series of experiments. Instead of a constant light-scattering intensity, he recorded a pattern that began as a maximum negative voltage and gradually decreased to a constant intensity value. (Tr. 580) Brittain opined that the initial maximum scattered light intensity was consistent with the fact that none of the cefadroxil had yet dissolved, and that the gradual decrease in intensity represented the dissolution of the Bouzard monohydrate until it reached an equilibrium, at which point the light scattering intensity remained constant. (Tr. 580; DX 16, pages 155-56)

In the next experiment, Brittain plotted scattered light intensities over time for light passed through simulated gastric juice in which he placed cefadroxil DC. The scattered light intensity curves he obtained in these experiments were more complex than in the other light scattering experiments. The initial intensity was not as great as the initial intensity of the Bouzard material suspended in the gastric juice. Brittain believed that this was consistent with the fact that cefradoxil DC crystals are smaller than Bouzard crystals, and hence would not refract as much light. (Tr. 581) Over the first minute, the scattered light intensity decreased, consistent with dissolution of the cefadroxil DC crystals into the gastric juice. (Tr. 581) At approximately one minute and eighteen seconds, however, the scattered light intensity increased steadily, surpassing the initial intensity, until the four and one-half minute mark, at which point the intensity remained relatively constant, decreasing only slightly. (Tr. 581) Brittain concluded from the fact that the final intensity was greater than the initial intensity that a definite change had occurred in the physical characteristics of the cefadroxil DC. (Tr. 581-82) This was consistent with his observations in other experiments that conversion to Bouzard had occurred. (Tr. 582) Brittain conducted microscopy experiments similar to those run in connection with the

first set of light-scattering experiments, in which he reproduced the conditions of the light scattering experiment —this time cefadroxil DC in simulated gastric juice—and took a series of microphotographs to record visual and birefringence changes in the crystals over time. (Tr. 587-88) Brittain observed that as early as 12 seconds into the experiment, Bouzard crystals were evident. (Tr. 588) From the strength of the birefringence of the crystals, and from the depth of the crystals, Brittain opined that evaporation could not have been the cause of the formation of the crystals. (Tr. 589)

7. *Sealed System Experiments*

A further set of experiments was performed in an attempt to minimize the effects that evaporation could have on cefadroxil solution observed microscopically. Brittain observed cefadroxil DC in simulated gastric juice placed in the well of a thick miscroscope slide over which he had placed a slide cover that was sealed with nail polish. (Tr. 593) This experiment was a standard laboratory technique for creating a sealed system that can be observed by microscope. (Tr. 593) Photomicrographs were taken at approximately two, four, six and eight minutes. (Tr. 594; DX 37) In each successive photograph, distinctive large triangular crystals believed by Brittain to be Bouzard crystals can be seen in greater quantity. (DX 37; Tr. 595)

Brittain conducted a second type of sealed system experiment, in which he filled test tubes that could be sealed by screwing on a threaded cap with cefadroxil DC in approximately 23 milliliters of water or simulated gastric juice. (Tr. 600-02) The goal of this experiment was to determine whether cefadroxil DC converted in a larger quantity of fluid in a sealed environment. (Tr. 601) Samples were maintained in a bath at 37°C and allowed to equilibrate for one half hour. (Tr. 601-02) Samples were then examined by microscopy and x-ray powder

diffration. Again, Brittain concluded that Bouzard crystals had formed. (Tr. 603, 605) These results were believed consistent with the sealed slide tests, and caused Brittain to conclude that evaporation played no role in the conversion of cefadroxil DC to Bouzard monohydrate. (Tr. 605)

8. *Freeze-Drying Experiments*

Brittain simulated the freeze-drying experiments of Dr. Greenblatt, with minor variations. He placed a Zenith cefadroxil DC capsule in 30 milliliters of simulated gastric juice maintained at 37°C and stirred at 10 rpm. (Tr. 606-07) At approximately two and three quarters minutes, instead of Dr. Greenblatt's one and three quarters minutes. Brittain removed the capsule from the dissolution apparatus and, within five to ten seconds, as opposed to Dr. Greenblatt's approximately five seconds, plunged the sample into liquid nitrogen. (Tr. 607) Dr. Brittain opined that the five second difference had no scientific significance. (Tr. 618)

After five minutes in the nitrogen, Brittain removed the sample and place it in a freeze-drying ("lyophilization") apparatus that he had constructed himself. (Tr. 608) The following day, he removed the contents and conducted microscopy and x-ray powder diffraction analyses of the sample. (Tr. 613) From these tests, Brittain concluded that the samples he observed contained Bouzard monohydrate. (Tr. 613)

Brittain conducted another experiment in which he replicated the dissolution and sample removal aspects of Dr. Greenblatt's experiment, removing the sample at one and three quarters minutes. (Tr. 619) He then sliced the capsule and performed microscopy and x-ray powder diffraction analyses of the contents. Brittain first observed that the contents of the capsule did not appear sufficiently wetted, in his opinion, for conversion to occur. (Tr. 620) The results of his microscopy examination

was that although some Bouzard crystals were present, the bulk of the sample was cefadroxil DC with weak birefringence. (Tr. 612) Likewise, the x-ray powder diffraction analysis yielded a pattern that signified to Brittain a mix of cefadroxil DC and Bouzard crystals. (Tr. 621-22) Brittain concluded that if a sample of cefadroxil DC is not sufficiently wetted, no conversion will occur. (Tr. 622-23)

9. *Gottstein Comparison*

To rebut Dr. Pfeiffer's testimony, Dr. Brittain made an independent comparison of the Gottstein and Zenith cefadroxil DC x-ray powder diffraction patterns. (Tr. 642) He concluded that the two patterns were on the border between being considered by him "similar" or "equivalent". (Tr. 642) From this, he did not believe that he could conclude that Gottstein would convert to Bouzard monohydrate. (Tr. 644-45)

Brittain recorded an x-ray diffraction pattern of a compound represented to him by Bristol to be Gottstein cefadroxil. When he compared the pattern obtained from the Bristol sample to the Marr pattern relied on by Dr. Pfeiffer, Brittain found that 21 of 24 peaks matched, and concluded that the patterns were equivalent. (Tr. 819-20) He then wetted 200 milligrams of the substance he believed was Gottstein cefadroxil and, after eight minutes, recorded another x-ray powder diffraction pattern. (Tr. 821) Brittain concluded from the second x-ray pattern that the Gottstein material had not changed, and that no Bouzard monohydrate could be detected. (Tr. 822) After another fifteen minutes had elapsed, which would have allowed evaporation to have occurred, he ran another powder pattern, which again remained unchanged. (Tr. 822-23) Yet another x-ray powder pattern was made after one hour had elapsed, with similar results. (Tr. 823) From this Britain concluded that Gottstein cefadroxil does not convert to Bouzard monohydrate when wetted. (Tr. 824)

C. *Zenith's Rebuttal Case*

Dr. Martha Greenblatt

Greenblatt was presented as a live witness on Zenith's rebuttal case. She testified that at the time of her initial experiments and deposition, she had not considered whether leaving the capsules in the simulated gastric acid for a longer period of time would have had any impact on the results of her tests. (Tr. 846) Since it was brought to her attention, Greenblatt had formed the opinion that leaving the capsules immersed for a longer period of time would not have changed her results, because the capsules had already opened and she believed that the capsules' contents had already been wetted. (Tr. 847) To verify this opinion, Greenblatt instructed a graduate student to conduct a further experiment in which he replicated her earlier experiments except that he increased the length of time in which the capsule remained in the gastric fluid before they were removed, from approximately two minutes to almost three minutes. (Tr. 864-65; PX 46) Greenblatt concluded that the results of this experiment were no different than the results of her earlier experiments—no conversion could be detected from the x-ray powder patterns. (Tr. 865)

Dr. Anthony P. Simonelli

Dr. Simonelli, the last witness to testify at trial, is a professor emeritus at the University of Connecticut. (Tr. 929) Dr. Simonelli performed no experiments of his own that were introduced at trial, but only gave his expert opinions based on the experiments of others. He was offered as an expert in biopharmaceutics, which is the study of how formulations of drugs interact with a biological environment/system (otherwise known as a body, be it human or other animal), and how changes in drug formulations affect their absorption by the biological system. (Tr. 929-30) Simonelli was also offered as an ex-

pert in the identification and analysis of polymorphic and solvate transformation in solid state and heterogeneous systems, and in the fields of nucleation and crystal growth, and x-ray diffraction analysis and optical microscopy (Tr. 931-33, 935)

Simonelli testified at length about the nucleation process that must precede any recrystallization of dissolved cefadroxil DC. He differed substantially with the theories of Dr. Brittain. Simonelli opined that Dr. Brittain's experiments did not prove that conversion occurred in the dissolution beaker. (Tr. 958) He instead believed that the recrystallization occurred on the microscope slide after a sample was removed from the beaker, because the conditions for nucleation and crystal growth are "fantastically higher on the slide than they are in the beaker," due to the greater saturation on the slide, (Tr. 959), and the cooling effect of evaporation, which aids precipitation of solids from a solution, (Tr. 980-81). Simonelli testified that Brittain's slide observations would not be representative of *in vivo* conditions, because evaporation and cooling, factors present on the slide that he believed greatly enhance crystal growth, are not present in the human stomach. (Tr. 981) He also believed that the stirring motion present in the stomach would diminish the possibility of nucleation and crystal growth. (Tr. 981) Simonelli further opined that other factors present in the stomach but not on a slide that might inhibit nucleation and crystal growth include the dissolved gelatin capsule, (Tr. 982-83), excipients, (Tr. 984), and the presence of macromolecules such as proteins and enzymes, (Tr. 1008, 1018).

Simonelli believed that Brittain's sealed system experiments are not conclusive because they at most eliminate only one factor as a possible explanation for the conversion: evaporation. (Tr. 986) He was at a loss to explain the difference in results between Dr. Brittain's and Dr. Greenblatt's second freeze-drying test results. He postu-

lated that the difference in time it took Brittain to remove the sample from the dissolution beaker and plunge it in the liquid nitrogen—at most five seconds—may account for the difference. (Tr. 987-88)

Simonelli opined that Brittain's light-scattering experiments also did not establish that conversion occurred in solution as opposed to on the slide, but were merely inconclusive. (Tr. 993, 995) He further opined that "sink" conditions present in the stomach would also inhibit nucleation and crystal growth. (Tr. 1012) According to Simonelli, sink conditions exist when the concentration of a compound is negligible in the bulk of a dissolution medium and is high near the surface of the compound being dissolved. (Tr. 1013-15) He believed that Dr. Lake-Bakaar was wrong in concluding that the rapidity of the conversion would counteract the sink effect, because he believes that the speed of the conversion does not affect the action of the sink conditions in preventing a localized supersaturation zone. (Tr. 1015-17) Simonelli conceded that the speed of the reaction is not unimportant, but, all else being equal, the presence of sink versus non-sink conditions would impact on the likelihood of nucleation and crystal growth. (Tr. 1017)

In general, Simonelli concluded that Brittain's experiments did not sufficiently simulate *in vivo* conditions to be indicative of nucleation and crystal growth in the human stomach. (Tr. 1008-09) He did not disagree with the conditions in the human stomach specified by Drs. Goldin and Lake-Bakaar, but disagreed that the beaker experiments of Dr. Brittain adequately accounted for other factors present in the stomach that would adversely affect the likelihood of conversion. (Tr. 1018-19)

II. *FINDINGS OF FACT*

The central fact issue that the Court must determine is whether the cefadroxil DC in Zenith's formulated capsules converts to Bouzard monohydrate *in vivo*. This

one issue was the focus of much scientific theorizing and experimentation, and has resulted in a trial record that contains a number of theories and abundance of data. A subsidiary issue that Zenith asserts circumscribes the breadth of the claim in the '657 patent is whether "Gottstein" cefadroxil is in fact cefadroxil DC, and whether Gottstein cefadroxil converts *in vivo* to the Bouzard monohydrate. This issue accounted for a minor portion of the evidence presented at trial.

A. *In Vivo Conversion*

Zenith's position on the conversion of cefadroxil DC into Bouzard monohydrate rests on the results it obtained from several experiments, and on expert opinion testimony that attempted to refute the results obtained by Bristol from its experiments. Zenith had three sets of experiments conducted to support its position that conversion does not occur.

First, Dr. Rothstein supervised an experiment to measure and compare the dissolution rates of cefadroxil DC and Bouzard monohydrate. Second, Dr. Rothstein supervised an experiment to measure and compare the equilibrium solubility and bulk density of those two compounds. Both the dissolution rates and equilibrium solubilities, as well as initial bulk densities, were found by Rothstein to be different for both compounds. In reliance on this data, Zenith expert Dr. Pfeiffer opined that conversion did not occur. His theory was that if cefadroxil DC first converted to Bouzard monohydrate before dissolving, the equilibrium solubility for the two materials would be identical, because in essence the same material would be dissolving into the dissolution medium.

The third set of experiments offered into evidence by Zenith were the freeze-drying experiments of Dr. Greenblatt. Greenblatt conducted two sets of experiments, differing only in the time at which the dissolving capsule was removed from the dissolution vat and frozen in liquid

nitrogen. The first set of experiments, with the shorter dissolution period, was offered into evidence on Zenith's direct case through deposition transcript with exhibits. The second set of experiments was offered into evidence on Zenith's rebuttal case through Greenblatt's live testimony and exhibits. The results obtained by Greenblatt were the [ ] same for both experiments: no conversion occurred.

Bristol's position with respect to Zenith's experiments is that they were scientifically inaccurate and otherwise flawed. Bristol's position on the conversion of cefadroxil DC into Bouzard monohydrate rests on the results it obtained from a number of experiments conducted by Dr. Brittain, and on expert opinion testimony that laid a foundation for some of the assumptions made by Brittain in attempting to simulate *in vivo* conditions. Drs. Levine and Goldin were offered as experts to support Bristol's position that actual *in vivo* experiments could not be conducted due to medical ethics constraints, and that no satisfactory *in vivo* experiment could be designed to test the conversion hypothesis that would be any more probative of the issue than are in *in vitro* experiments of Dr. Brittain. Drs. Goldin and Lake-Bakaar were offered as experts in gastroenterology to lay the foundation for the conditions utilized by Dr. Brittain to simulate conditions inside the human stomach.

The bulk of Bistol's evidence consists of the numerous experiments conducted by Dr. Brittain to verify that cefadroxil DC converts to Bouzard monohydrate. Brittain designed and conducted a variety of experiments to test different aspects of the conversion issue, all of which confirmed in his opinion that conversion would in fact occur *in vivo*. Zenith's position with respect to Bristol's experiments is that they at best prove that conversion occurs on a microscope slide under conditions different from those present in the human stomach. Zenith's experts opined that Bristol did not even prove that conversion occurs in a dissolution beaker, much less *in vivo*.

The Court finds that Bristol presented by far the more compelling case on the issue of conversion.

1. *Use of In Vitro Experiments*

The opinions of Drs. Levine and Goldin that, given the nature of the experiments which would be required, *in vivo* experimentation could not be justified under medical ethics constraints merely to prove patent infringement, stands unrefuted by Zenith. Both doctors were adequately qualified to give this opinion and were credible witnesses. Therefore, the Court finds that Bristol's use of *in vitro* experiments to establish *in vivo* events is in principle a valid methodology. *Cross v. Iizuka,* 753 F.2d 1040, 1050 [224 USPQ 739] (Fed. Cir. 1985); *Nelson v. Bowler,* 626 F.2d 853, 856 [206 USPQ 881] (C.C.P.A. 1980).

2. *Validity of Brittain's Simulated In Vivo Conditions*

The conditions prescribed by Drs. Goldin and Lake-Bakaar to simulate conditions in the human stomach, i.e., 30 milliliters of simulated or actual gastric juice maintained at 37°C and stirred at three to ten rpm, were also unrefuted by Zenith. Further substantialy unrefuted was Dr. Lake-Bakaar's opinion that the emptying rate of the stomach and the secretion rate of additional gastric juice are sufficiently slow in comparison to the rate at which Brittain believed conversion occurred such that failure to account for those factors would not constitute a flaw in Brittain's experiments. Both doctors were adequately qualified to give these opinions and were credible witnesses. Therefore, to the extent Bristol established the occurrence of conversion under these conditions that was not attributable to some other condition present in the *in vitro* experiment that is not present *in vivo,* it has proved that *in vivo* conversion also would occur.

3. *Brittain's Experiments*

Dr. Brittain spent far more time on the witness stand during this trial than did any other witness. Over the course of nearly three full days of testimony, the Court had the opportunity to observe and listen to Brittain at great length. The Court's impression of Dr. Brittain is that he is a talented research chemist, who possesses a significant ability to thoroughly understand a problem and, through his broad knowledge of laboratory instrumentation, design multiple experiments to test many aspects of that problem. He was also, for the most part, a very credible witness.

Dr. Brittain's explanation of the *reason* that conversion occurs, and the *process* by which it occurs, however, seemed to be somewhat beyond the scope of his expertise. On this point, Zenith's Dr. Simonelli seemed more knowledgeable. In fact, though, the Court does not believe that any witness presented in this case has anything more than a superficial understanding of the "mechanism" or "pathway" by which conversion occurs. At issue in this case, however, is not "why" conversion occurs, but only "whether" it occurs. Thus, although Dr. Brittain's explanation of the conversion process seemed beyond the ken of his expertise and was somewhat lacking in credibility, the Court finds that Brittain has established by a preponderance of evidence, well within his range of expertise, that cefadroxil DC in fact converts *in vivo* to Bouzard monohydrate.

The strength of Brittain's experiments and results is their totality. Piece by piece, Brittain built an impressive collection of data. The results of each series of experiments strengthen the results of each other set of experimental results. The total effect of the experiments is to prove with sufficient certainty the fact of conversion *in vivo*.

In support of its motion for summary judgment, Zenith submitted expert affidavits that concluded that the pro-

tonation of cefadroxil DC molecules dissolved in gastric acid would prevent recrystallization of dissolved cefadroxil DC. At trial, Bristol introduced testimony and test results by Brittain to refute this claim. Those experiments tested for protonation, and the results indicated that protonation did not occur. Zenith offered no evidence at trial to refute this evidence. Accordingly, the Court finds that protonation plays no role in inhibiting conversion.

The largest number of experiments conducted by Brittain were the dissolution experiments in which he placed both bulk powder or formulated capsules in varied amounts of water or simulated or actual gastric juice and later tested the samples for conversion. The dissolution medium volume and stirring rate conditions employed encompassed and exceeded the wide range of possible conditions *in vivo*. Through the use of three tests—visual observation, birefringence comparison and x-ray diffraction pattern comparison—Brittain concluded uniformly that under any of the conditions used, he detected conversion.

Brittain first established indisputably through photomicrography that cefadroxil DC crystals are much smaller than Bouzard monohydrate crystals, and are much different in shape. He also established that cefadroxil DC crystals exhibit a much weaker birefringence than do crystals of Bouzard monohydrate, which are highly birefringent. Thus, through microscopy, Brittain could determine with a high degree of certainty whether a sample of wetted cefadroxil DC had changed its crystalling form, and could conclude to a lesser extent that the form to which it had changed was Bouzard monohydrate. Although changes in the physical properties of shape, size and birefringence of the cefadroxil DC crystals could be conclusively determined through microscopy, Britain could not determine by observation alone that the larger, more birefringent crystals were necessarily Bouzard. To determine conversion to Bouzard with great certainty, Brittain ran x-ray powder diffraction patterns, a technique that in essence takes the "fingerprint" of a crystalline compound.

Through x-ray diffraction analysis, Brittain determined with much greater confidence that all of the conversions suspected after optical examination had in fact been to Bouzard monohydrate.

Zenith contends that Brittain failed to establish that any of the x-ray diffraction patterns, including his Bouzard monohydrate reference pattern, conform to the x-ray diffraction pattern that forms the claim of the '657 patent. The Court disagrees, with respect to the reference pattern, Bristol has put into evidence numerical tables representing both the patent pattern and Brittain's reference pattern. (DX 1; DX 16 at 19) According to Zenith's own expert, Dr. Pfeiffer, differences of 0.2 or less are insignificant in comparing x-ray diffraction patterns. (Tr. 233) According to Dr. Brittain, whose expertise on X-ray powder diffraction pattern analysis the Court accepts, patterns with at least a 95% match of peaks are "identical" compounds. (Tr. 633). Using Dr. Pfeiffer's margin of error, a simple comparison of the tables reveals that 21 out of 22 peaks in the patent pattern are matched by peaks in Brittain's reference pattern. Although Pfeiffer would find a "match" even with a variation of up to 0.2, most of the matches have differences of less than 0.05. In fact, only one match even approaches, but does not exceed 0.1. Thus, there are 21 clear matches out of 22 peaks in the patent pattern. The ratio of 21/22 exceeds the 95% peak matches Brit[t]ain would require to conclude that two compounds are identical. The Court thus concludes that Zenith's claim that Brittain's reference pattern is not of the same compound claimed in the '657 patent is without any merit.

The Court further finds credible Brittain's conclusions that the patterns obtained from wetted cefadroxil samples recovered from his experiments are equivalent to the reference pattern for Bouzard monohydrate. Dr. Brittain's expertise with the analysis and comparison of x-ray diffraction patterns was amply demonstrated, and the Court accordingly adopts Brittain's conclusions. Zenith's assertion

that the comparison are inconclusive because Brittain concluded only that the patterns were "equivalent" and not "identical" is rejected by the Court. Although under Brittain's rating system "identical" is the higher rating, the Court accepts Brittain's opinion that a finding of "equivalance" is sufficient to support his conclusion that conversion had occurred. The standard of proof in this case is not the "beyond a reasonable doubt" standard.

The Court finds that Brittain's laboratory procedures for the dissolution experiments were consistent, well-documented and highly credible. Zenith has not with any force directly refuted the results of Brittain's microscopy and x-ray diffraction tests. Zenith's criticisms of Brittain's results are based on contentions that the conversion occurred not in the dissolution beaker, but on the microscope slide, under conditions greatly different from actual *in vivo* conditions. Alternatively, Zenth contends that even if conversion does occur in the beaker, the beaker conditions are significantly different from *in vivo* conditions. The Court finds these contentions also without merit.

A major basis for Zenith's contention that conversion occurs on a slide and not in a beaker or the stomach is that on the slide, a much more saturated solution exists, which Dr. Simonelli opined was much more conducive to nucleation and crystal growth. The Court finds that Bristol demonstrated with a high degree of certainty that conversion occurs *inside* of an ingested capsule, and that the environment inside of a capsule penetrated by gastric liquid would be of a similar or greater saturation level to that existing on a slide. Thus, the Court finds that Zenith's distinction between beaker and slide conversion is meaningless to the extent it is based on differences in saturation levels. To the extent that the beaker/slide argument is premised on conditions present on a slide that are not also present inside of a capsule ingested *in vivo*, it has adequately been overcome by Bristol's affirmative proofs.

Zenith, through Drs. Simonelli and Pfeiffer, posited that several material differences exist between the conditions present on a slide and those present *in vivo,* which impact greatly on the question of *in vivo* conversion. First, both Pfeiffer and Simonelli identified evaporation and cooling as two factors present on a slide but not in the stomach. They opined that evaporation is conducive of cooling, which is conducive of precipitation of crystals out of solution. As will be discussed below, Brittain conducted experiments that refuted the significance of either of these factors.

Simonelli and Pfeiffer further opined that the stirring action and replenishment of fluids in the stomach would adversely affect the occurrence of nucleation and crystal growth. Dr. Simonelli assumed that conversion occurs *after* the cefadroxil DC leaves the capsule, because the "dynamic situation" he discussed was based on the movement of the capsule contents as they poured out of the capsule. (Tr. 981) Dr. Pfeiffer's opinion was similarly flawed. Because the Court finds that conversion occurs inside of an ingested capsule, it finds that stomach agitation as an inhibitor of conversion is of minimal significance, and opinions relying on it are not entitled to much, if any, weight. Further, the Court finds that Simonelli's suggestion that the replenishment of fluids in the stomach is similarly without credibility. Dr. Lake-Bakaar's testimony as to the extremely slow rate of stomach emptying and replenishment was highly credible and stands unrefuted. The Court therefore finds Simonelli's opinion as to this factor to be lacking in credibility.

Other factors identified by Simonelli as existing in the stomach but not on a slide include the presence of gelatin, excipients and macromolecules such as food particles, proteins and enzymes. The Court finds this testimony to be worthy of no weight.

First, on cross-examination, Simonelli conceded that macromolecules such as food particles or proteins could

enhance nucleation and crystal growth, as well as inhibit them. (Tr. 1026-27) Second, excipients were present on the slide as well as *in vivo* in those dissolution experiments conducted by Brittain that used Zenith capsules. Dr. Simonelli's attempted explanation of why excipients would have a lesser impact on a slide than they would in a capsule, (Tr. 984), seemed contrived and lacked credibility. Third, macromolecules of the variety identified by Simonelli were present on the slide in those dissolution experiments conducted by Brittain that used actual gastric juice. Last, Simonelli's testimony that dissolved gelatin may inhibit nucleation and crystal growth, though probably true in the abstract, does little to refute the results of Brittain's experiments. According to Simonelli, Brittain's experiments failed to account for the presence of gelatin because his samples were taken from the inside of the capsule. (Tr. 983) Because the Court finds that conversion occurs inside the capsule, it finds Simonelli's criticism to lack merit.

Yet another factor Simonelli identified as present in the stomach but not on a slide was "sink" conditions. Simonelli's opinion, however, was premised on conversion occurring outside of the capsule, in a low concentration solution. Because the Court finds that conversion occurs inside of the capsule, this factor is of little consequence. Moreover, Brittain demonstrated that conversion occurs even under conditions that Simonelli agreed would constitute sink conditions. (Tr. 1022-23) Although Dr. Simonelli impressed the Court as a scientist of distinction with vast experience, his opinion testimony in this case was not supported by any experimental data, was in good measure highly speculative in nature, and did not cast significant doubt on Bristol's experimental evidence of conversion.

One of several series of experiments conducted by Brittain to verify the occurrence of conversion in the dissolution beaker instead of on a slide, free from the effect of

evaporation and cooling, was Brittain's series of light-scattering experiments. Those experiments cast great doubt on Zenith's contention that conversion occurs only as a result of the greater saturation levels, cooling and evaporation present on a slide.

Although Zenith contends that the light-scattering experiments do not prove beaker conversion because the saturation levels in the cuvettes used in those experiments were closer to slide saturation conditions than to beaker saturation conditions, this argument is not supported by the record. The light-scattering experiments used 25 milligrams of cefadroxil DC placed in a cuvette holding three milliliters of simulated gastric juice. This represents a ratio of solvate to solvent only one half that of the ratio of solvate to solvent that existed in Brittain's dissolution experiments that used 500 milligrams of cefadroxil DC in capsule form placed in 30 milliliters of simulated gastric juice. If, as Zenith contends, conversion does not occur inside the capsule because its contents leave too rapidly, then the resulting solution would be adequately proxied by the cuvette in the light-scattering experiments. Accordingly, to the extent that the light-scattering experiments prove conversion inside the cuvette, they also prove beaker conversion.

The scattered light traces recorded by Brittain are also highly corroborative of Brittain's opinion that conversion occurs free from the effects of evaporation and temperature cooling. Through several runs of the light-scattering experiment, Brittain established that undissolved Bouzard monohydrate crystals floating in a dissolution medium maintained at a constant temperature scatter more light than do undissolved cefadroxil DC crystals. This is consistent with the greater size and birefringence of Bouzard monohydrate crystals.

The Court finds that the trace at page 157 of Brittain's laboratory notebook (DX 16) establishes that conversion occurred in the cuvette, as opposed to on the slide. There,

the undissolved cefadroxil DC initially placed in simulated gastric juice reflected a certain intensity of light, before it diminished and then, at approximately one minute, gradually increased in intensity, reaching a level in excess of the initial level of scattered light. This trace proves without question that some physical change occurred inside the cuvette. Dr. Brittain opined that this curve is consistent with an initial dissolution phase in which the scattered light intensity declined as the cefadroxil DC dissolved, and then increased as conversion occurred and Bouzard crystals precipitated out of solution, resulting in a scattered light intensity exceeding the initial intensity reflected by Cefadroxil DC crystals. The Court finds this explanation highly credible and corrobarative of Brittain's other experiments.

Further corraborative of the occurrence of conversion before a sample was placed on a slide, and perhaps more revealing, are the series of photomicrographs recorded by Dr. Brittain over time under the conditions used in the light scattering experiments. Over time, Dr. Brittain observed greater numbers in larger sizes of Bouzard-shaped crystals. The appearance of these crystals in the photographs is identical to crystals observed in other experiments in which they were identified by x-ray diffraction analysis as Bouzard crystals. Accordingly, the Court finds credible Brittain's conclusion that these crystals were also Bouzard crystals. The increase and size and quantity of Bouzard crystals over time in the photographs would not be possible if, as Zenith contends, conversion occurred on the slide. Instead, each slide would have an equal amount of Bouzard crystals of equal size. Therefore, the Court finds that this experiment further buttresses the conclusion that conversion occurs even under conditions free from the effects of evaporation and cooling.

The Court finds that Dr. Brittain's light-scattering experiments were highly probative of the issue of conversion

in solution versus on the slide. Zenith's only witness who addressed the results of this experiment, Dr. Simonelli, had no adequate explanation for these results. His conjecture that an aggregation and dispersion of cefadroxil DC particles, or the presence of excipients in the solution may have been the cause of changes in light-scattering intensity was speculative, and unsupported by any experimental data or literature, and is accorded little weight.

The Court also finds that Brittain's sealed system experiments prove that evaporation played little, if any, role in the microscopy observation made by Brittain. By sealing slides and test tubes, and then recording conversion over time, Brittain has refuted Zenith's claim. If evaporation played a significant role in the observed conversion, a sealed slide or test tube system should contain only those converted crystals that had already precipitated out of solution before the slide was sealed. Instead, Brittain observed continuing precipitation of Bouzard crystals long after the slide was sealed. Thus, the Court finds that evaporation, a condition that both parties agree does not exist in the stomach, was not a substantial cause, if it was a cause at all, of conversion on the microscope slide.

Last, Brittain's freeze-drying experiments also corroborate his other findings that conversion occurs inside of a capsule cefadroxil DC capsule if enough time is allowed to elapse. His findings will be compared to those of Dr. Greenblatt below.

4. *Greenblatt's Freeze-Drying Experiments*

Differences between Dr. Greenblatt's first series of freeze-drying experiments and Dr. Brittain's freeze-drying experiments could be accounted for by differences in the length of time that capsules were left in the dissolution beakers before being removed and frozen. The results of Greenblatt's second series of experiments, however, appear to directly conflict with the results of Brittain's

experiments. The Court finds unlikely, and unsupported by credible evidence, Zenith's suggestion that a difference of at most five seconds between the length of time it took Greenblatt to remove a capsule from the beaker and place it in liquid nitrogen and the length of time it took Brittain to do the same could account for the difference in results. Zenith's own witness, Dr. Pfeiffer, opined that a difference of two or three seconds would be insignificant. (Tr. 188-89) The Court also finds unlikely Bristol's suggestion that grinding and desiccation of the recovered sample could cause converted Bouzard to revert to cefadroxil DC, a more unstable form of cefadroxil. Thus, the Court can only resolve this conflict by resort to an evaluation of credibility. On this count, the Court must conclude, on the basis of its observations of both witnesses and scrutiny of their testimony, that Brittain's results are significantly more credible. Brittain demonstrated repeatedly during trial his consistency in laboratory method, his understanding of the problem he was investigating, his knowledge of laboratory equipment and the ability to design and verify experiments. By contrast, although she may have significant expertise in fields of inquiry unrelated to the issues in this case, Greenblatt demonstrated little understanding of the problem at issue in this case or the reason for her procedures and thus played no role in the design of her experiments, lacked any prior experience in freeze-drying techniques, was lax in her methodology, particularly in the recording of her procedures and observations, and in fact did not even participate in the second series of experiments. The Court finds that Brittain's freeze-drying results are simply better supported and vastly more credible. Accordingly, those findings are adopted by the Court.

5. *Rothstein's Dissolution Rate and Equilibrium Solubility Experiments*

Zenith contends that Dr. Rothstein's experiments prove that conversion does not occur. Specifically, Zenith con-

tends that the observed differences in dissolution rates between cefadroxil DC and Bouzard monohydrate are inconsistent with conversion, because if conversion occurred within the capsule, similar equilibrium solubility results would be observed after the contents of the capsule were released and dissolved into solution. For this conclusion, Zenith relies on the testimony of Dr. Pfeiffer, and an article from a medical journal annexed as Exhibit B to Defendant's Exhibit 13. (Tr. 92)

Though the Rothstein results may support Zenith's position that conversion does not occur, the Court does not find that those results overcome the extensive proofs contained in Brittain's experiments. The Court is hard-pressed to reconcile the conflict between Rothstein's experimental results and Brittain's. An explanation proffered by Bristol is that the Rothstein results are inconclusive because of the possibility of a significant degree of experimental error. The margins of error recorded by Rothstein with respect to the dissolution rate experiments support Bristol's contention. (See Tr. 54; PX 21) The absence of any effort by Rothstein to account for margin of error as to the equilibrium solubility experiments leaves the issue unresolvable. On the basis of the trial record, the Court can neither conclude that the experiment results are tainted by error, nor exclude experimental error as an explanation for the discrepancy. Thus, at bottom, the Court can only find that the powerful proofs by Bristol of the occurrence of conversion are simply much more persuasive, and greatly outweigh the Rothstein results, from which the non-occurrence of conversion is merely a possible inference.

B. *Gottstein Findings*

A subsidiary fact issue raised by Zenith is whether cefadroxil DC is in fact a form of cefadroxil prior in the art to Bouzard monohydrate. Zenith contends that this issue bears on the interpretation of the claim in the '657 patent, and on the ultimate issue of infringement. Based

on its review of the evidence, the Court finds that Zenith has adequately demonstrated that Gottstein cefadroxil and cefadroxil DC are similar crystalline forms of cefadroxil. The Court finds, however, that although the x-ray diffraction patterns of Gottstein cefadroxil is similar to the x-ray diffraction pattern for cefadroxil DC, Bristol has proved that cefadroxil DC converts to Bouzard monohydrate when wet, and that Gottstein cefadroxil does not.

The only evidence Zenth relies on to support its position that the two materials are the same is Dr. Pfeiffer's comparison of the two respective compounds' x-ray diffraction patterns, and his opinion that, based solely on this comparison, if one material converted, the other would also. This opinion is completely refuted by the results of an experiment in which Brittain attempted without success, under conditions stated by Zenith's experts to be highly conducive of conversion, to make Gottstein convert to Bouzard monohydrate. Given this result, in contrast to Brittain's proof that cefadroxil DC converts to Bouzard monohydrate, the Court finds that Gottstein cefadroxil is distinctly different from cefadroxil DC. Zenith's further contention that Bristol has not proved that the material it claims is in fact Gottstein materials is also without merit. Brittain relied on a comparison of an x-ray diffraction pattern that he obtained from his Gottstein sample with the same pattern Zenith relied on as representative of Gottstein, and concluded credibly that his Gottstein sample matched the Gottstein pattern relied on by Zenith. The Court finds that Bristol has proved that the material it used to test for conversion was in fact Gottstein cefadroxil.

III. *CONCLUSIONS OF LAW*

A. *Jurisdiction and Burden of Proof*

Count I of Zenith's complaint arises under the patent laws of the United States, 35 U.S.C. §§ 1 *et seq.* For reasons stated by the Court on previous occasions, a justiciable controversy has existed and continues to exist

between the parties. Therefore, the Court has subject matter jurisdiction over this action pursuant to 28 U.S.C. § 1338(a).

As a declaratory judgment plaintiff, Zenith had the burden to prove the existence of an actual controversy, which in this case required proof that Bristol posed a threat that it would sue Zenith for infringement based on acts in which Zenith had a present intention and capacity to engage. *Indium Corp. of America v. Semi-Alloys, Inc.*, 781 F.2d 879, 883 [228 USPQ 845] (Fed. Cir. 1985), *cert. denied*, 479 U.S. 820, 107 S. Ct. 84 (1986). This burden was met. As a patent owner who has been proved in a declaratory judgment action to have posed a threat to sue for infringement, Bristol bears the burden to prove infringement. *Advance Transformer Co. v. Levinson*, 837 F.2d 1081, 1084 [5 USPQ2d 1600] (Fed. Cir. 1988) (trial court did not err in finding that patent owner-defendant in declaratory judgment action had not met his burden to prove infringement); *United Sweetener USA, Inc. v. Nutrasweet Co.*, 760 F. Supp. 400, 417 [19 USPQ2d 1561] (D. Del. 1991); *Deere & Co. v. Sperry Rand Corp.*, 322 F. Supp. 397, 398 [168 USPQ 150] (E.D. Cal. 1970), *aff'd*, 513 F.2d 1131 [185 USPQ 495] (9th Cir.), *cert. denied*, 423 U.S. 914, 96 S. Ct. 218 [191 USPQ 240] (1975); *see also* E. Borchard, Declaratory Judgments 404-09 (2nd ed. 1941); *Under Sea Industries, Inc. v. Dacor Corp.*, 833 F.2d 1551, 1557 [4 USPQ2d 1772] (Fed. Cir. 1987) ("The burden is always on the patentee to show infringement"). Infringement must be proved by a preponderance of evidence. *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 758 [221 USPQ 473] (Fed. Cir. 1984).

B. *Direct Infringement*

There are two forms of infringement, literal infringement and infringement under the doctrine of equivalents. "Literal infringement requires that every limitation of the patent claim must be found in the accused device." *Uni-*

royal, Inc. v. Rudkin-Wiley Corp., 837 F.2d 1044, 1054 [5 USPQ2d 1434] (Fed. Cir.), *cert. denied*, 488 U.S. 825, 109 S. Ct. 75 (1988). Infringement under the equitable doctrine of equivalents comes into play when, although there is no literal infringement, the accused device performs substantially the same function, in substantially the same way, to achieve substantially the same result. *Graver Tank & Mfg. Co. v. Linde Air Products Co.*, 339 U.S. 605, 608, 70 S. Ct. 854, 856-57 [85 USPQ 328] (1950); *Uniroyal*, 837 F.2d at 1057.

Because it is undisputed that the cefadroxil DC product Zenith intends to manufacture and sell would not, in its manufactured form, literally infringe the '657 patent, Bristol relies on the doctrine of equivalents to support its allegations of direct infringement by Zenith. Specifically, Bristol relies on a line of cases in which non-infringing materials that convert *in situ* to claimed materials or materials used in a claimed process have been held to infringe under the doctrine of equivalents. *See Atlas Powder Co. v. E. I. Du Pont de Nemours & Co.*, 750 F.2d 1569 [224 USPQ 409] (Fed. Cir. 1984) (affirming finding that oil-in-water emulsifying agent that converted to water-in-oil emulsifying agent *in situ* constituted infringement of claimed water-in-oil emulsion); *Chemical Cleaning Corp. v. Dow Chemical Co.*, 379 F.2d 294 [155 USPQ 49] (5th Cir. 1967) (affirming finding that monomethylthiourea, which disassociated during process to form thiourea, was equivalent of thiourea), *cert. denied*, 389 U.S. 1040, 88 S. Ct. 777 [156 USPQ 719] (1968); *Broadview Chemical Corp. v. Loctite Corp.*, 159 U.S.P.Q. 80 (D. Conn. 1968) (finding formation of quinone as result of chemical reaction during use of sealant made sealant equivalent of patented quinone-containing sealant), *aff'd in relevant part*, 406 F.2d 538 [160 USPQ 449] (2d Cir.), *cert. denied*, 394 U.S. 976, 89 S. Ct. 1472 [161 USPQ 832] (1969); *Studiengesellschaft Kohle, M.B.H. v. Dart Industries, Inc.*, 549 F. Supp. 716 [216 USPQ 381] (D. Del. 1982) (finding use of catalyst

formed during process infringed claims directed to use of pre-formed catalysts under doctrine of equivalents), *aff'd*, 726 F.2d 724 [220 USPQ 841] (Fed. Cir. 1984). More closely on point, Bristol has directd the Court's attention to two cases that involved "pro drugs", which are drugs that convert *in vivo* to a patented form of drug. *See Ortho Pharmaceutical Corp. v. Smith*, 18 U.S.P.Q.2d 1977 (E.D. Pa. 1990), *aff'd*, 959 F.2d 936 [23 USPQ2d 1119] (Fed. Cir. 1992); *Beecham Group Ltd. v. Bristol Laboratories Ltd.*, [1978] R.P.C. 153 (House of Lords 1977) (finding infringement of patent under English doctrine of "pitch and marrow"). The findings of infringement in these cases were based on the doctrine of equivalents and its English counterpart. These cases support Bristol's position.

Zenith makes three arguments against the Court finding infringement under the doctrine of equivalents. It claims first that Bristol has not proved that cefadroxil DC performs the same function in substantially the same way to achieve substantially the same results. In connection with this argument, it claims that the "heart" or "essence" of the '657 patent resides in the manufacturing advances allowed by the greater bulk density and stability of Bouzard monohydrate.

The Federal Circuit Court of Appeals has observed that although the "heart of the invention" doctrine, which it characterized as "dicta," may be useful in determining infringement under the doctrine of equivalents, it should not be used to ignore limitations in a patent claim. *Perkin-Elmer Corp. v. Westinghouse Electric Corp.*, 822 F.2d 1528, 1533 n.8 [3 USPQ2d 1321] (Fed. Cir. 1987). Analogously, the Court finds that the "heart of the invention" dicta should also not be used to improperly read additional limitations into a claim.

Zenith would have the Court apply the "heart of the invention" doctrine to read limitations into claim 1 of the '657 patent constricting the scope of uses, purposes or functions of Bouzard monohydrate protected by the pat-

ent. The claim contains no such limitations, express or implicit; it claims the Bouzard monohydrate *per se*. A patent holder's rights are defined by the claims in its patent. *Corning Glass Works v. Sumitomo Electric U.S.A. Inc.*, 868 F.2d 1251, 1257 [9 USPQ2d 1962] (Fed. Cir. 1989). The sole function of a claim is "to point out distinctly the process, machine or composition of matter which is patented, not its advantages." *Preemption Devices, Inc. v. Minnesota Mining and Manufacturing Co.*, 732 F.2d 903, 907 [221 USPQ 841] (Fed. Cir. 1984). Bristol has the right to exclude others from *all* uses of the Bouzard monohydrate. *See Roberts v. Ryer*, 91 U.S. 150, 157 (1875) ("The inventor of a machine is entitled to the benefit of all the uses to which it can be put"); *American Standard, Inc. v. Pfizer, Inc.*, 722 F. Supp. 86, 103 [14 USPQ2d 1673] (D. Del. 1989) ("an inventor is entitled to all applications to which his invention can be put to use, including those not mentioned in the specification"); 4 *Chisum on Patents* § 16.02[4] at 16-27 to -28 (1991) ("One does not escape infringement by using a patented invention for a purpose not contemplated or disclosed by the patentee"). The use of Bouzard monohydrate as an antibiotic is expressly stated in the patent specification. Because the Court has found that cefadroxil DC converts *in vivo* to Bouzard monohydrate before it is absorbed into the bloodstream to act as an antibiotic, the Court finds that it necessarily performs the same function in substantially the same way to achieve substantially the same result.

Second, Zenith contends that the range of equivalents to Bouzard monohydrate may not be extended to cefadroxil DC because to do so would "ensnare" prior art. *See Wilson Sporting Goods Co. v. David Geoffrey & Assoc.*, 904 F.2d 677, 684 [14 USPQ2d 1942] (Fed. Cir.), *cert. denied*, 111 S. Ct. 537 (1990). This argument is predicated on a finding of fact that cefadroxil DC is the same compound as Gottstein cefadroxil. Because the Court has found otherwise, this argument fails.

Last, Zenith contends that prosecution history estoppel precludes a finding that cefadroxil DC is an equivalent of Bouzard monohydrate. *See Pennwalt Corp. v. Durand-Wayland, Inc.*, 833 F.2d 931, 934 n.1 [4 USPQ2d 1737] (Fed. Cir. 1987) (en banc) ("patentee may not recapture through equivalence certain coverage given up during prosecution"), *cert. denied*, 485 U.S. 961, 1009 (1988). The Court agrees.

Prosecution history estoppel is an affirmative defense to patent infringement. *Insta-Foam Products, Inc. v. Universal Foam Systems, Inc.*, 906 F.2d 698, 703 [15 USPQ2d 1295] (Fed. Cir. 1990). Zenith contends that, because Dr. Bouzard relied on the superior manufacturing advantages of Bouzard monohydrate to distinguish it from the prior art, and the patent was granted only because of those characteristics, those manufacturing advantages limit the range of equivalents of the claimed invention by estoppel. Accordingly, it claims that because none of the manufacturing advances on which Bouzard predicated patentability of Bouzard monohydrate would be utilized by Zenith in its production of cefadroxil DC capsules, Bristol is estopped from contending that cefadroxil DC is an equivalent compound.

Prosecution history estoppel "prevents a finding of infringement even though the substituted structure is in fact equivalent." *Read Corp. v. Portec, Inc.*, —— F.2d ——, Slip Op. at 7, 1992 WL 158788 [23 USPQ2d 1426] (Fed. Cir. July 10, 1992). Under the doctrine of prosecution history estoppel:

> a patentee cannot "recapture through equivalence certain coverage given [by argument or amendment] during prosecution." That is not to say, however, that, whenever a limiting amendment or argument is made during prosecution, the patentee loses all coverage between what the claims literally cover and what they would have covered prior to the amendment or argument. Instead, "[d]epending on the

nature and purpose of an amendment, it may have a limiting effect within a spectrum ranging from great to small to zero.["]

Hormone Research Foundation v. Genentech, Inc., 904 F.2d 1558, 1564 [15 USPQ2d 1039] (Fed. Cir. 1990). Reliance on superior utility over the prior art to establish non-obviousness thus would not necessarily limit the scope of the invention to its use for those purposes. *In re Chupp*, 816 F.2d 643, 647 [2 USPQ2d 1437] (Fed. Cir. 1987) (patentee need not demonstrate superiority of all uses of claimed invention over prior art to obtain patent covering those uses). "Every statement made by a patentee during prosecution to distinguish a prior art reference does not create a separate estoppel. Arguments must be viewed in context." *Read Corp.*, Slip Op. at 7.

It is undisputed that Bouzard expressly distinguished Bouzard monohydrate from the prior art solely on the basis of its superior manufacturing characteristics. Although during prosecution of the patent, Bouzard submitted a declaration to the Patent and Trademark Office that concluded that Bouzard monohydrate had a greater therapeutic value than was found in the prior art forms of cefadroxil, see Declaration of Edel Berman dated July 9, 1979, this conclusion was subsequently withdrawn through the Declaration of Edel Berman dated December 17, 1984, submitted as part of an amendment to the application on December 30, 1984, after it was discovered that the conclusion was inadequately supported by scientific evidence. The patent examiner entered the amendment "as directed to matter of form not affecting the scope of the invention" because he concluded that the therapeutic value of Bouzard monohydrate "was never a factor in determining patentability." Report of Patent Examiner Mark Berch dated February 13, 1985.

The Court finds that, through argument to the Patent Office, Bouzard narrowed the range of equivalents of Bouzard monohydrate. Because patentability was predi-

cated solely on the manufacturing properties of the Bouzard monohydrate, the Court finds that the range of equivalents that may be found to infringe the '657 patent is limited to compounds that are equivalent in the manufacturing characteristics on which patentability was solely predicated. Thus, unlike in *Read Corp.*, where the court found that a certain feature "in itself was never asserted to be the basis for patentability over [prior art]", Slip Op. at 7, here, the only "feature" of Bouzard monohydrate—its superior manufacturing characteristics—was asserted as the basis for patentability. The range of equivalents that can infringe is therefore accordingly limited.

This case is easily distinguishable from the two "prodrug" cases relied by Bristol. In both cases, the patent in issue covered a compound in any and all forms, not just one form of the compound as does the '657 patent. The range of equivalents covered by the patents were therefore, unlike in this case, appropriately broad enough to cover equivalent structures created *in vivo*. Moreover, the issue of prosecution history estoppel was neither raised nor addressed in those two cases.

Because Zenith has established by a preponderance of evidence that the range of equivalents covered by the '657 patent is limited to equivalent structures that infringe on the manufacturing characteristics on which patentability of the '657 patent was based, the Court finds that cefadroxil DC as manufactured does not directly infringe the '657 patent under the doctrine of equivalents.

C. *Induced Infringement*

Alternatively, Bristol contends that Zenith's proposed sales of cefadroxil DC would constitute inducement of infringement under 35 U.S.C. § 271(b).[6] "A person induces infringement by actively and knowingly aiding

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[6] That section provides: "Whoever actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. § 271(b).

and abetting another's direct infringement." *C.R. Bard, Inc. v. Advanced Cardiovascular Systems, Inc.*, 911 F.2d 670, 675 [15 USPQ2d 1540] (Fed. Cir. 1990); *H.B. Fuller Co. v. Nat'l Starch and Chemical Corp.*, 689 F. Supp. 923, 943 [7 USPQ2d 1753] (D. Minn. 1988). Given the Court's finding that cefadroxil DC converts *in vivo* to Bouzard monohydrate, if absorption of the converted drug into the bloodstream by a person constitutes a "use" within the meaning of 35 U.S.C. § 271(a), then the person ingesting cefadroxil DC would literally infringe the '657 patent. Consequently, any sale of cefadroxil DC by Zenith for human consumption, in light of the findings in this opinion, would constitute a direct and knowing inducement of that infringement. Thus, the critical issue, disputed by the parties, is whether absorption of converted Bouzard monohydrate by a person who ingests cefadroxil DC constitutes a "use" within the meaning of the infringement statute.

Zenith has raised several arguments against finding absorption of converted Bouzard monohydrate to constitute an infringing "use." Zenith first contends that such "uses" are not covered by the literal terms of the claim in the '657 patent. Its places great reliance to support this argument on the claim language, which states that the patent covers crystalline monohydrate "*exhibiting* essentially the following x-ray diffraction properties." (Emphasis added), *see supra* at note 1. It contends that the word "exhibiting" requires that the patent be construed to apply only to pre-ingested forms of Bouzard cefadroxil, because x-ray diffraction properties can only be "exhibited" through x-ray diffractometry, which cannot be performed on ingested cefadroxil. The Court rejects this tortured reading of the claim language. The logic of this argument, if followed, would constrict the patent claim to apply to nothing other than bulk unformulated powder. Based on the evidence received at trial, it appears that x-ray diffraction analysis cannot be performed on

cefadroxil contained inside of a capsule. To read the claim as Zenith does would thus render Bouzard monohydrate placed inside of a capsule outside the scope of the patent, an absurd result.

Zenith also asserts that the claim should be construed narrowly not to extend to ingested forms of Bouzard cefadroxil, so that it does not read on prior art. *See Whittaker Corp. v. UNR Industries, Inc.*, 911 F.2d 709, 712 [15 USPQ2d 1742] (Fed Cir. 1990) (claim should be construed to uphold its validity). This argument, as with a similar argument raised in connection with the doctrine of equivalents, is predicated on a finding that cefadroxil DC is the same as Gottstein cefadroxil and is thus prior art. Because the Court has found that the factual predicate for this argument is invalid, this argument is also without merit.

The second argument made by Zenith why absorption of converted cefadroxil does not constitute an infringing "use" is that such "use" of Bouzard monohydrate is too insignificant and removed from the purpose for which the patent was allowed to fall within the statutory meaning of the term. Zenith relies on *Kaz Mfg. Co. v. Chesebrough-Ponds, Inc.*, 317 F.2d 679 [137 USPQ 588] (2d Cir. 1963), and asserts that the case holds that a use does not infringe unless the user gains the benefits of the teachings of the patent. *Id.* at 680 and n.3. The Court disagrees with this reading of *Kaz*.[7]

Kaz involved the use by defendant in a television advertisement of a steam vaporizer constructed by combining parts from two different models of steam vaporizers manufactured by plaintiff. *Id.* at 680. Defendant had

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[7] Accordingly, the Court disagrees with the interpretation of *Kaz* in *Roche Products, Inc. v. Bolar Pharmaceutical Co.*, 572 F. Supp. 255, 258 (E.D.N.Y. 1983), *rev'd*, 733 F.2d 858 [221 USPQ 937] (Fed. Cir.), *cert. denied*, 469 U.S. 856 [225 USPQ 792] (1984).

purchased the two vaporizers from a retailer. *Id.* In this Court's view, the opinion in *Kaz* rests on a ground that does not support Zenith's argument. Although not stated expressly in the opinion, this Court reads *Kaz* to rest on a finding that the "use" made by defendant of the vaporizers was permissible under an implied license granted to defendant with the purchase of the vaporizers. *See United States v. Univis Lens Co.*, 316 U.S. 241, 250-52, 62 S. Ct. 1088, 1093-94 [53 USPQ 404] (1942) (first sale by a patentee of an article embodying his invention exhausts his patent rights in that article) *Met-Coil Systems Co. v. Korners Unlimited, Inc.*, 803 F.2d 684, 687 [231 USPQ 474] (Fed Cir. 1986). This reading of *Kaz* is supported by the court's statements that the vaporizers "were sold by plaintiff without restrictions", *Kaz*, 317 F.2d at 680, and that "the only right retained by the plaintiff, once it sold the patented vaporizers, was the right to be free from competition 'in the practice of the invention' ", *id.* at 681 (citation omitted). Zenith cannot contend that it has any license rights, implied or otherwise, under the '657 patent. Therefore, the Court concludes that *Kaz* is inapposite to the issue of "use".

The Federal Circuit Court of Appeals has not considered in any depth the breadth of "use" that is covered by 35 U.S.C. § 271(a). Its most detailed exposition on the subject is its statement in *Roche Products, Inc. v. Bolar Pharmaceutical Co.*, 733 F.2d 858 [221 USPQ 937] (Fed. Cir.), *cert. denied*, 469 U.S. 856 [225 USPQ 792] (1984) (superseded by statute), that:

> Because Congress has never defined use, its meaning has become a matter of judicial interpretation. Although few cases discuss the question of whether a particular use constitutes an infringing use of a patented invention, they nevertheless convincingly lead to the conclusion that the word "use" in section 271(a) has never been taken to its utmost possible scope.

Id. at 861. In support of this statement, the Federal Circuit cited to cases recognizing an "experimental use" exception and the notion of implied license to use or sell a purchased patented article. As neither of these recognized constraints on the scope of the term "use" is in issue in this case, the Court concludes that it is bound to apply the Supreme Court's holding in *Roberts* that an inventor "is entitled to the benefit of all the uses to which" a patented invention can be put. *Roberts*, 91 U.S. at 157; *see also American Standard*, 722 F. Supp. at 103; 4 *Chisum* § 16.02[4] at 16-27 to -28.

Zenith's argument that the *in vivo* use of converted cefadroxil DC should not be found infringing under a *de minimis* exception to the bar against infringing uses codified in § 271(a) has facial appeal. This case presents circumstances under which it might be appropriate to adopt such an exception. The only courts to address the issue, however, are of limited authority. The trial court in *Roche Products* held that a drug used in connection with an FDA application did not infringe under a *de minimis* exception; that judgment was reversed by the Federal Circuit. *Roche Products, Inc. v. Bolar Pharmaceutical Co.*, 572 F. Supp. 255, 258 (E.D.N.Y. 1983), *rev'd*, 733 F.2d 858 [221 USPQ 937] (Fed. Cir.), *cert. denied*, 469 U.S. 856 [225 USPQ 792] (1984). The case relied on by the trial court in *Roche Products* for the existence of a *de minimis* exception was a Seventh Circuit opinion in which the exception was discussed in *dicta*, and in any event was factually much different from this case in that it involved a remote sale of one arguably infringing article where there was no threat of future infringement. *See Maxon Premix Burner Co., Inc. v. Eclipse Fuel Eng'g Co.*, 471 F.2d 308, 317 [175 USPQ 324] (7th Cir. 1972). In the absence of more guidance from the Federal Circuit on the meaning of the term "use" in § 271(a), as indicated above, the Court believes it is bound by the United States Supreme Court's statement in *Roberts*.

Zenith further argues that no "use" literally occurs because the converted Bouzard crystals dissolve into solution before they are absorbed into the bloodstream to act as an antibiotic. Though true, the same is also true of cefadroxil that exists as Bouzard monohydrate before it is dissolved. Many drugs taken orally work by dissolving *in vivo* to be absorbed into the bloodstream. Zenith's argument, if adopted, would essentially bar all claims of "infringing use" involving any drug defined in the patent by its crystalline structure.

Zenith also contends that literal infringement by a user of converted Bouzard monohydrate is precluded by the reverse doctrine of equivalents. That doctrine derives from the Supreme Court's decision in *Graver Tank & Manufacturing Co. v. Linde Air Products Co.*, 339 U.S. 605, 70 S.Ct. 854 [85 USPQ 328] (1950), in which the Court stated

> where a device is so far changed in principle from a patented article that it performs the same or a similar function in a substantially different way, but nevertheless falls within the literal words of the claim, the doctrine of equivalents may be used [in reverse] to restrict the claim and defeat the patentee's action for infringement.

Id. at 608-09, 70 S.Ct. at 856-57. It thus allows a court to find noninfringement when an alleged infringer has proved that "even if the claim literally read on the accused device it has been so changed that it is no longer the same invention." *Del Mar Avionics, Inc. v. Quinton Instrument Co.*, 836 F.2d 1320, 1325 [5 USPQ2d 1255] (Fed. Cir. 1987). In essence, the doctrine operates to restrict a claim in a patent by limiting the "range of products" that fall within its literal language. *SRI Int'l v. Matsushita Electric Corp. of America*, 775 F.2d 1107, 1125 & n.22 [227 USPQ 577] (Fed. Cir 1985) (en banc). An accused infringer has the burden to establish noninfringement under the doctrine. *Id.* at 1123-24.

According to the Federal Circuit Court of Appeals, "a defense based on the reverse doctrine of equivalents is rarely offered", because products that fall within the literal terms of a patent claim are often in fact the same in substance as is described by the claim. *Id.* at 1123 n.19. To sustain a defense under the reverse doctrine of equivalents requires proof that the accused product "is in fact a different product." *Phillips Petroleum Co. v. United States Steel Corp.*, 673 F. Supp. 1278, 1357 [6 USPQ2d 1065] (D. Del. 1987), *aff'd*, 865 F.2d 1247 [9 USPQ2d 1461] (Fed. Cir. 1989).

The Federal Circuit has noted the conceptual difficulties inherent in applying the reverse doctrine of equivalents to a patent claim for a chemical compound, such as is involved in this case. *United States Steel Corp. v. Phillips Petroleum Co.*, 865 F.2d 1247, 1253 n.9 [9 USPQ2d 1461] (Fed. Cir. 1989). That court questioned how one can even conceptualize, under the language of the doctrine, a way to determine whether a chemical compound that falls *literally* within the claim of a patent can perform the same "function" in a substantially different "way" as that disclosed in the claim. *Id.* For such products, there is very little leeway to determine that a product *literally* reads on the claim but is so far changed in principle from the claimed compound that it does not infringe.

When a patent claims only a very specific chemical molecular structure—as does the '657 patent, which claims one specific crystalline form of cefadroxil monohydrate—an accused compound that literally infringes is not easily susceptible to the reverse doctrine of equivalents. The '657 patent claims the specific crystalline form of the compound *per se*. As the accused converted compound has been found to consist of the identical molecular structure specifically claimed in the patent, there is no escaping literal infringement. Bristol has proved that the converted cefadroxil DC both falls within the literal language of the claim, and in fact *is* the claimed compound.

Zenith's "reverse equivalents" argument is based on its contention that Bristol predicated patentability solely on certain manufacturing advantages achieved by the newly-discovered and claimed Bouzard monohydrate crystal form. Thus, it argues, because none of the manufacturing advantages of the Bouzard monohydrate are realized by cefadroxil DC when it allegedly converts to the Bouzard monohydrate *in vivo*, cefadroxil DC is not the same invention as the Bouzard monohydrate. Although the Court has found that prosecution history estoppel limits the range of equivalents that may be found to infringe, it declines to find that the reverse doctrine of equivalents limits the scope of literal infringement. Because the converted compound is indistinguishable in any way from the patented compound, the doctrine simply has no applicability.

Accordingly, the Court concludes that use of converted Bouzard monohydrate by a patient who ingests cefadroxil DC is an infringing use. Therefore, the sale of cefadroxil DC by Zenith would constitute inducement of infringement under 35 U.S.C. § 271(b).

D. *Remedy*

Bristol asserts that because it has sustained its burden of proof to establish infringement of cefadroxil DC, for which Zenith has obtained FDA approval, it is entitled to the remedy prescribed in 35 U.S.C. § 271(e)(2)(A):

> The court shall order the effective date of any approval of the drug . . . involved in the infringement to be a date which is not earlier than the date of the expiration of the patent which has been infringed. . . .

The Court agrees. Zenith's contention that such relief should not be granted because Bristol did not assert a counterclaim seeking such relief is without merit. The statute provides that such relief "shall" be ordered when an act of infringement is established. As Bristol has sustained its burden of proof on inducement of infringement,

indirect infringement has been established. Accordingly, the Court is without discretion to deny the requested relief and will therefore grant it.

CONCLUSION

For the reasons stated above, the Court finds that the sale of cefadroxil DC would [] constitute inducement of infringement of the claim in the '657 patent. The attorneys for Bristol are requested to submit an appropriate form of order.

APPENDIX C

DISTRICT COURT
D. NEW JERSEY

No. 91-3423

ZENITH LABORATORIES, INC.

v.

BRISTOL-MYERS SQUIBB CO.

August 6, 1992

OPINION

Wolin, J.

A six-day bench trial of the infringement claim in this case occurred in May and June 1992. The infringement claim was severed from the other claims in the case and heard on an expedited basis due to the imminence of Zenith Laboratories, Inc. ("Zenith") marketing its cefadroxil DC "product" [1], for which FDA approval was granted in April 1992. In its Opinion dated April 13, 1992, the Court indicated that the trial was to encompass the issue "whether cefadroxil DC converts to the Bouzard monohydrate *in vivo*." Opinion at 12. The Court issued its findings of fact and conclusions of law on July 21, 1992. In that opinion, the Court determined that although cefadroxil DC does not as manufactured directly infringe the '657 patent-in-suit, sales of that drug by Zenith would constitute inducement of infringement, because the drug

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[1] In its Amended Complaint, Zenith refers repeatedly to cefadroxil DC in the singular as its "cefadroxil product".

would convert *in vivo* to the drug claimed in the '657 patent.

In its July 21, 1992 Opinion, the Court requested that Bristol-Myers Squibb ("Bristol") submit an appropriate form of judgment order. Both Bristol and Zenith submitted proposed orders, and objections to each other's proposed order. This Letter Opinion will explain the basis for the Court's rejection of Zenith's proposed order and its overruling of Zenith's objection to Bristol's proposed order.

Bristol submitted a proposed order that would: (1) enter judgment in its favor on Count I of Zenith's amended complaint; (2) order and declare that the sale by Zenith of cefadroxil DC would constitute an act of infringement under 35 U.S.C. § 271; and (3) order that the effective date of Zenith's Food and Drug Administration approval shall not be earlier than the expiration data of the '657 patent. Zenith has objected to only one aspect of this proposed order, and has submitted its proposed order. Zenith contends that Bristol is entitled only to a declaration that Zenith's cefadroxil DC *capsules* would infringe the '657 patent.

Zenith further contends that it is entitled to a declaration that its cefadroxil DC *tablets* would not infringe the patent-in-suit. Bristol has objected to this proposal on the ground that no distinction was ever made between capsules and tablets by either party, and that in any event Bristol proved that the tablets infringe.

Zenith's suggestion that it is entitled to a declaration of non-infringement as to its tablets, coming as it is only *after* the Court issued its findings of fact and conclusions of law, must be rejected. No meaningful distinction was ever made at trial between cefadroxil DC capsules and tablets. The only evidence presented at trial that Zenith can point to related to its tablets was a dissolution test performed on tablets by Dr. Rothstein. Dr. Rothstein's tests were found by the Court to be inconclusive and

possibly tainted by experimental error. See July 21, 1992 Opinion at 53-54. Thus, to the extent Zenith even placed the distinction between tablets and capsules in issue, it did not meet its burden to come forward with a *prima facie* case as to the non-infringement of its tablets.

Most important, however, is that Zenith was given an ample opportunity to bring the distinction between tablets and capsules to the Court's attention, to the extent it was supported by the trial record, in its proposed findings of fact and conclusions of law. Zenith submitted extensive proposed fact findings that it contended were proved at trial. Glaringly absent, in view of Zenith's current contention, is *any* proposed finding that distinguished between tablets and capsules. The only mention of tablets was in Zenith's proposed finding of fact No. 12, in which Zenith proposed that the Court find only that "Zenith's AADA supplements for cefadroxil capsules and tablets utilizing raw material supplied by Gema were approved on April 21, 1992." In its proposed ultimate finding on the issue of conversion, Zenith proposed that the Court find that "Zenith cefadroxil DC capsules do not convert to a different crystal form under *in vitro* conditions designed to simulate *in vivo* conditions." Zenith's Proposed Findings of Fact No. 83. No similar proposed finding was submitted respecting Zenith's cefadroxil DC tablets.

The Court accommodated the parties by scheduling an expedited trial. Zenith was on notice that the trial was intended to encompass *all* issues related to the infringement count of Zenith's complaint, and specifically to the *in vivo* conversion of cefadroxil DC, in any form, to the form of cefadroxil claimed in the '657 patent. Zenith therefore had an obligation to bring to the Court's attention any and all arguments, factual and legal, that had any significant bearing on the trial of the issue of infringement, at the risk of losing the right to assert any argument not raised at trial under principles of *res judi-*

cata. The distinction between Zenith capsules and tablets was never effectively put in issue by Zenith.

Although Bristol bore the burden of proof at trial on the issue of infringement, Zenith is nevertheless the plaintiff in this declaratory judgment action, and bore the burden to come forward with evidence sufficient to raise the issue of infringement. It never did so with respect to raising an issue as to the difference between capsules and tablets. It therefore cannot now claim that because all of Bristol's proofs were directed to capsules, Bristol is only entitled to a declaration limited to capsules. Nor can it now claim that it is entitled to a declaration of non-infringement as to the tablets. By its inaction until after the Court issued its findings of fact and conclusions of law, Zenith has waived its right to make the argument that there is a difference between its capsules and tablets. The Court will therefore enter an order similar in form to that submitted by Bristol.

ORDER

In accordance with the Court's Opinion filed July 21, 1992,

It is on this 6th day of August, 1992,

ORDERED that judgment is entered in favor of defendant on Count I of plaintiff's Amended Complaint; and it is further

ORDERED AND DECLARED that the ingestion of cefadroxil DC by patients infringes United States Patent No. 4,504,657 ("the '657 patent") and, thus, the sale of cefadroxil DC by Zenith Laboratories, Inc. ("Zenith") would constitute an act of infringement of the '657 patent under 35 U.S.C. § 271, and it is further

ORDERED that the effective date of Zenith's Food and Drug Administration approvals issued on April 21, 1992 for Zenith's cefadroxil product shall not be earlier than March 12, 2002, the expiration date of the '657 patent.

APPENDIX D

[Filed May 26, 1994]

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

92-1527

ZENITH LABORATORIES, INC.,
Plaintiff-Appellant,

v.

BRISTOL-MYERS SQUIBB COMPANY,
Defendant-Appellee.

ORDER

A combined petition for rehearing and suggestion for rehearing in banc having been filed by the APPELLEE, and a response thereto having been invited by the court and filed by the APPELLANT, and the petition for rehearing having been referred to the panel that heard the appeal, and thereafter the suggestion for rehearing in banc and response having been referred to the circuit judges who are in regular active service,

UPON CONSIDERATION THEREOF, it is

ORDERED that the petition for rehearing be, and the same hereby is, DENIED and it is further

ORDERED that the suggestion for rehearing in banc be, and the same hereby is, DECLINED.

The mandate of the court will issue on June 2, 1994.

Circuit Judge NEWMAN would rehear the appeal in banc. Chief Judge ARCHER did not participate in the vote.

FOR THE COURT
FRANCIS X. GINDHART
Clerk

By /s/ Diane M. Frye
DIANE M. FRYE
Chief Deputy Clerk

Dated: May 26, 1994

cc: WILLIAM L. MENTLIK
S. LESLIE MISROCK

APPENDIX E

SUPREME COURT OF THE UNITED STATES

No. A-65

BRISTOL-MYERS SQUIBB COMPANY,
Petitioner

v.

ZENITH LABORATORIES, INC.

ORDER

UPON CONSIDERATION of the application of counsel for the petitioner,

IT IS ORDERED that the time for filing a petition for a writ of certiorari in the above-entitled case, be and the same is hereby, extended to and including September 14, 1994.

/s/ William H. Rehnquist
WILLIAM H. REHNQUIST
Chief Justice of
the United States

Dated this 28th day of July, 1994.